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ELECTROCARDIOGRAPHIC ABNORMALITIES IN SEVERE MALNUTRITION

BY

LAURENCE B. ELLIS

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Just before and after V-E day a major medical problem in the European Theatre of Operations was the care of the great number of liberated Allied prisoners of war. Many of these were suffering from profound and prolonged malnutrition and the gravity of their physical condition, coupled with the great numbers involved, taxed the resources of the medical personnel caring for them. Numerous studies of various aspects of the physiological derangements of these soldiers have been made. This report is concerned with electrocardiographic findings in a small series of severely malnourished patients.

During the night of April 24, 1945, a trainload of 300 fresh casualties reached a U.S. Army General Hospital in England. Among these were a few severely malnourished liberated American prisoners of war. One of these, S/Sgt. A. A., appeared to be in such a critical state that it seemed unlikely that he would survive many hours. He was semi-stuporous, so weak he could hardly lift a hand, emaciated to a degree which has become all too familiar in photographs of the " Horror Camps," and suffering from intense diarrhœa. In spite of this he showed no œdema, his blood pressure was normal, and there was no clinical evidence of any vitamin deficiency. On admission it was noted that his pulse rate was 40 at the wrist and about 60 at the apex. This led to the taking of a cardiogram the following morning. Because of the striking findings in this record (Fig. 1), serial records were made on this patient and on 13 other liberated prisoners who were the most severely malnourished.

Some days after admission the first patient was interviewed by a reporter from the *Stars and Stripes*. Excerpts from this interview are reproduced here as they depict in graphic terms the conditions which produced the physical state of all of these men.

U.S. GENERAL HOSPITAL. The day the Nazis took S/Sgt. A.A., 106th Infantry Division squad-leader, prisoner, he weighed 210 pounds. Five months later, when liberated, he weighed 116 pounds. Considering the hell he's been through, he is coming along fine. But thanks to Himmler's S.S. he won't be walking around for some time. Here's what he told me :

" I was captured at St. Vith during the Rundstedt breakthrough. The Nazis searched me, and put me in a box-car with 42 other Yanks. They locked us in, sending us on our way to Germany.

" For five days and nights we didn't have any food or water. Luckily, some of our fellows still had a little water in their canteens—just enough to wet 43 parched mouths. We didn't dare drink the stuff; it was too precious. Added to this, the convoy we were in was being bombed and strafed continually by the Allies.

" We were sent to Camp 4b, 50 miles south of Berlin, and then to Camp 8a, near Gorlitz. Camp 4b was better to us. At least they didn't abuse us so much. Finally, they started us on the march because the Russians were advancing We got very little to eat on the march, but we usually got plenty of water. If there weren't any rivers or streams around the Russians or " Froggies " always brought it to us in buckets. If our guards caught them, they used to beat them, but most of them were smart. They used to leave the buckets on the side of the road and hide until we went by.

" I don't remember just how far we'd marched when the Yanks caught up with us. What I do remember, I was lying on top of a straw and manure pile when they found me, and I was pretty well gone."

Clinical abstracts on this and three other patients showing the most striking electrocardiographic changes follow.

Case Notes

Case 1. Staff Sgt. A. A., 29 years old, was captured on December 19, 1944, and released on April 13, 1945, eleven days before he entered the hospital. In addition to the account of his experiences quoted above, the following information is relevant. While a prisoner he had lived on the regular prison diet, which consisted of a sixth to an eighth of a loaf of bread, soup which occasionally contained a little meat, and a few potatoes daily. In addition, while marching, he received some jam and one-ninth of a tin of meat weekly. In spite of his steady loss of weight he got along pretty well until February, since which time he was almost constantly on the march, averaging about 20 kilometres a day. Three days before he was liberated he developed diarrhœa and abdominal cramps, and very rapidly went down hill from then on. He lost weight estimated at 100 lb. while a prisoner.

His past history was irrelevant; he was always a very healthy and vigorous person. Physical examination showed extreme emaciation, weakness, and semi-stupor. There was no œdema nor any evidence of vitamin deficiency. His tongue was normal and his skin though dirty showed no evidence of hyperkeratosis. The lungs were clear, the heart sounds were faint, and there was an apical systolic murmur. His blood pressure was 110 mm. systolic and 60 mm. diastolic.

Laboratory findings are shown in Table I. In addition the plasma albumin was 3·6 and globulin 2·0 per 100 c.c. on May 5. Urine analysis was normal except for a one-plus albumin on entry. A radiogram of the chest showed the lung fields to be clear and the heart unusually small, and one of the hands and forearms showed no evidence of decalcification. Cardiograms are shown in Fig. 1, 2, and 3.

TABLE I

Laboratory and Cardiographic Findings on Cases 1–4

Case No.	Date	Hæmoglobin Grams /100 c.c.	Plasma proteins Grams /100 c.c.	Serum Ca. mg. /100 c.c.	Serum P mg. /100 c.c.	Electrocardiograms			
						P–R interval sec.	QRS interval sec.	Q–T interval * sec.	T waves
1	April 25	13·3	6·2			0·19–0·20	0·12	0·70 (+0·28)	T II TIII up with low origin †
	April 30			10·2	1·5	0·19	0·11	0·60 (+0·18)	T II TIII diphasic with low origin T IV diphasic
	May 3					0·19	0·09	0·50 (+0·14)	T II T III diphasic
	May 5	10·9	5·6	10·2	3·2				
	May 8					0·19	0·08	0·38	T II up T III inverted
	May 16					0·18	0·07	0·33	All T waves upright
2	April 25	13·5	6·7			0·21	0·09	0·52 (+0·14)	T I T II T IV bifid
	April 28					0·18	0·08	0·54 (+0·16)	T IV bifid
	April 30			9·5	1·6	0·22	0·08	?0·50	T IV bifid
	May 5		5·1	8·7	3·3				
	May 8					0·18	0·08	0·37	All T waves upright
3	April 25	16·8	8·0						
	April 29					0·12	0·08	?0·48 (+0·14)	T I isoelectric T II T III inverted
	May 3	14·9		9·0	1·5	0·12	0·08	0·48 (+0·14)	T II T III low origin
	May 7					0·12	0·08	0·34 (+0·02)	Slight depression S–T II and T III
	May 16					0·12	0·07	0·32	All T waves upright
4	April 26	11·1	5·5			0·14	0·07	0·38 (+0·04)	Bifid T IV
	May 5			9·1	4·0				
	May 10					0·14	0·06	0·33	Normal T waves

* Figures in parentheses refer to increase in Q–T above the maximum allowable by the standards of Ashman (1942). Measurements were made from start of QRS to return to the iso-electric level after the T waves and may include U waves.

† Ventricular premature beats every third beat.

His diarrhœa and cramps continued for about a week. For the first few days he was unable to take nourishment by mouth, except in extremely small quantities. He was given 2 units of plasma and 1000 c.c. of 5 per cent glucose in normal saline solution daily for three days. His temperature, which was sub-normal on entry, rose to 103 degrees by May 2 and remained up for several days, although at this time he had very greatly improved. He gained an estimated 20 lb. during this first week, this being largely due to improvement in hydration. On May 4 he was allowed to sit in a chair and by May 16 to walk short distances. He was given a 500 c.c. blood transfusion on May 8.

Case 2. Pte. B. P., 23 years old, was captured on December 21, 1944, and released on April 13, 1945. His history was very similar to that of the first patient. The diet he was given was exactly the same and he suffered from severe diarrhœa for about two weeks before his release. Physical

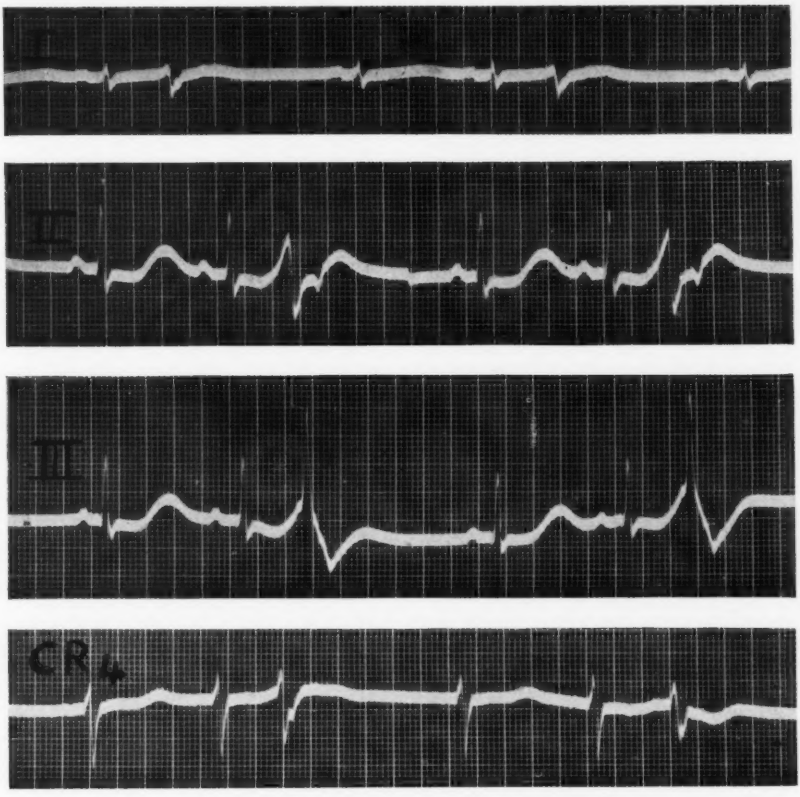

FIG. 1.—Electrocardiogram of Case 1. 25/4/45.

examination showed extreme malnutrition with an estimated loss of 64 lb. in weight during his confinement. He, however, was admitted as an ambulatory patient and was perfectly clear mentally. Physical examination on entry showed no œdema nor signs of vitamin deficiency. The heart was normal on examination, with normal sounds and no murmurs. Blood pressure was 110/70.

Laboratory findings are shown in Table I. In addition the urine analysis was normal, except for a one-plus albumin on entry. The plasma albumin was 4·1 on April 25 and 3·5 on May 5, and the globulin 2·6 and 2·1 per 100 c.c. on the same dates. A radiogram of his heart showed it to be rather small, and one of his hands and forearms showed no evidence of decalcification. Fig. 4 shows the cardiograms.

By April 30 he was much better and his diarrhœa had ceased. He was eating well, as he had since the beginning of his stay in hospital, and never required any intravenous fluid administration. On April 30 he developed some œdema of the ankles which persisted for about ten days. On this date also he noted that he had cramps of the hands and legs, and when he tried to write, his right hand went into spasm. Examination revealed carpo-pedal spasm after exercising his hands or feet and a positive Trousseau sign but a negative Chvostek sign. There were some fibrillary twitchings in the forearms. These signs persisted for about four days. At this time his blood calcium was normal, he was well hydrated and there was no clinical evidence of alkalosis, but the carbon dioxide combining power of the blood could not be done. His improvement continued thereafter in an uninterrupted manner, except that on May 16 he developed mild jaundice which was interpreted as being due to infectious hepatitis. This persisted for about a week only.

Case 3. Cpl. R. D., 25 years old, was captured on December 19, 1944, and released April 16, 1945. His history was much like the others except that he had not been forced to undergo any marching during the months before his release. He had had diarrhœa for about a week before his release. Upon entry he appeared to be in fair physical condition but had lost 30 lb. in weight. The blood

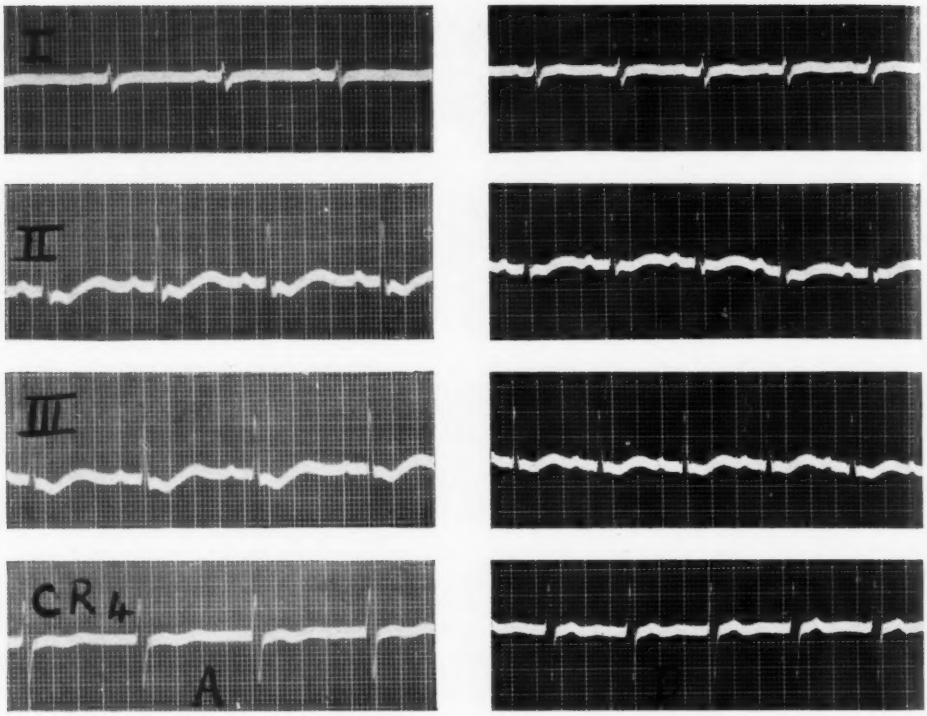

FIG. 2.—Later electrocardiograms of Case 1. (A) 30/4/45. (B) 3/5/45.

pressure was 90/50 and the pulse rate ranged between 100 and 120. There was no œdema and no clinical evidence of vitamin deficiency. Examination of the heart was normal.

Besides the laboratory findings shown on Table I, the urine analysis was normal and a radiogram of the heart showed it to be rather small. The cardiograms are shown in Fig. 5.

On April 27 his clinical condition was worse. He became very weak and developed nausea and vomiting and his blood pressure became unobtainable by the auscultatory method, but was estimated at about 80 mm. systolic by palpation. He was given 2 units of plasma and 1000 c.c. of 5 per cent glucose in normal saline solution. This parenteral treatment was continued daily for four days. By May 2 he was much better and his blood pressure had risen to 120/70. He was then eating well without any more vomiting and his diarrhœa had practically ceased. His improvement after this continued uninterruptedly.

Case 4. Pte. J. B., 25 years old, was captured January 8, 1945 and released April 20, 1945. His story was similar to the others. He was marched for about 25 kilometres a day during the two weeks just before liberation and during this time also suffered from diarrhœa. In addition he gave a story of having had intermittent swelling of the hands and feet and around his eyes from March until shortly before he was admitted. He lost 55 lb. in weight during his confinement. Physical examination except for his emaciation was essentially normal. Examination of his heart revealed normal sounds and no murmurs were heard. The blood pressure was 120/70. There was no œdema and no clinical evidence of vitamin deficiency.

Laboratory findings are shown in Table I. In addition examination of the urine was negative except for a minimal amount of albumin on entry. The plasma albumin was 3·7 and the globulin 1·8 per 100 c.c. on April 26. A radiogram of the heart showed it to be well within normal limits. His cardiograms are shown in Fig. 6.

He ran a temperature for several days ranging from 103 to 104 degrees, with no evidence of any infection. His course in the hospital was uneventful and consisted of steady improvement.

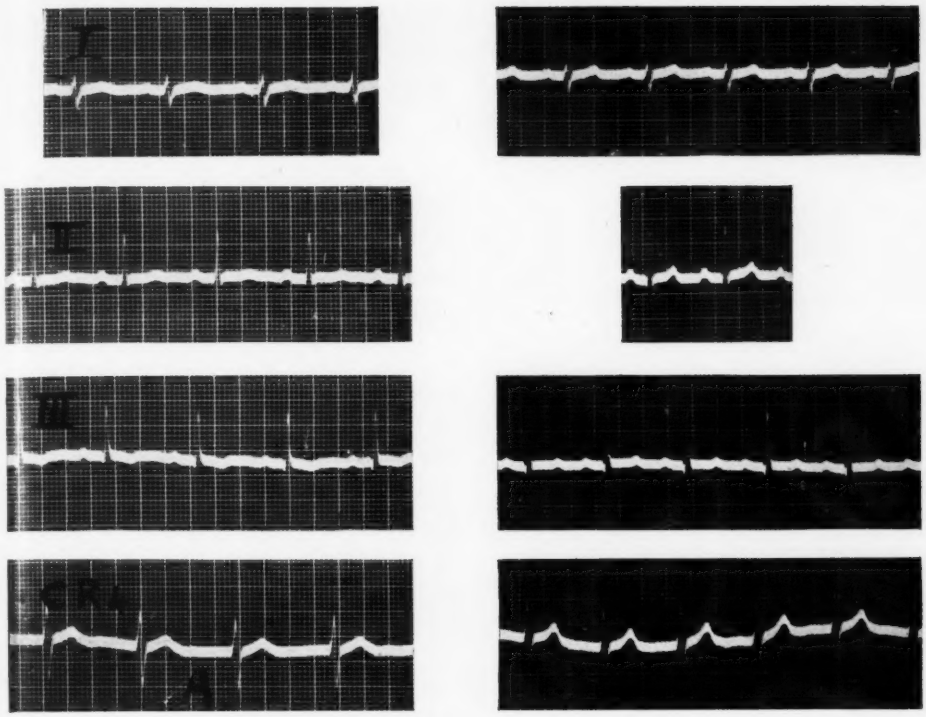

FIG. 3.—Later electrocardiograms of Case 1. (A) 8/5/45. (B) 16/5/45.

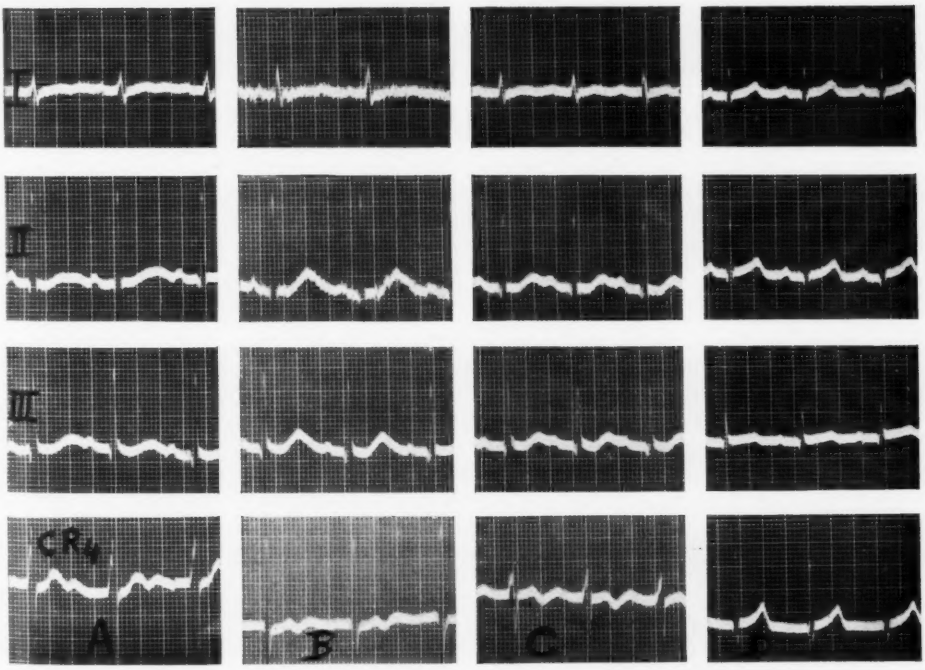

FIG. 4.—Electrocardiograms of Case 2. (A) 25/4/45. (B) 28/4/45. (C) 30/4/45. (D) 8/5/45.

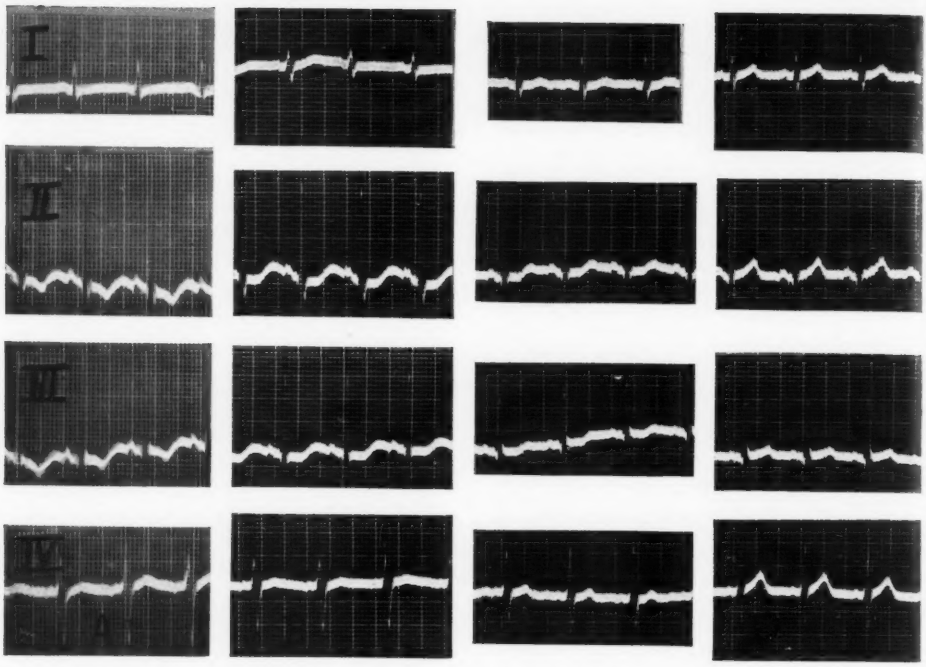

FIG. 5.—Electrocardiograms of Case 3. (A) 29/4/45. (B) 3/5/45. (C) 7/5/45. (D) 16/5/45.

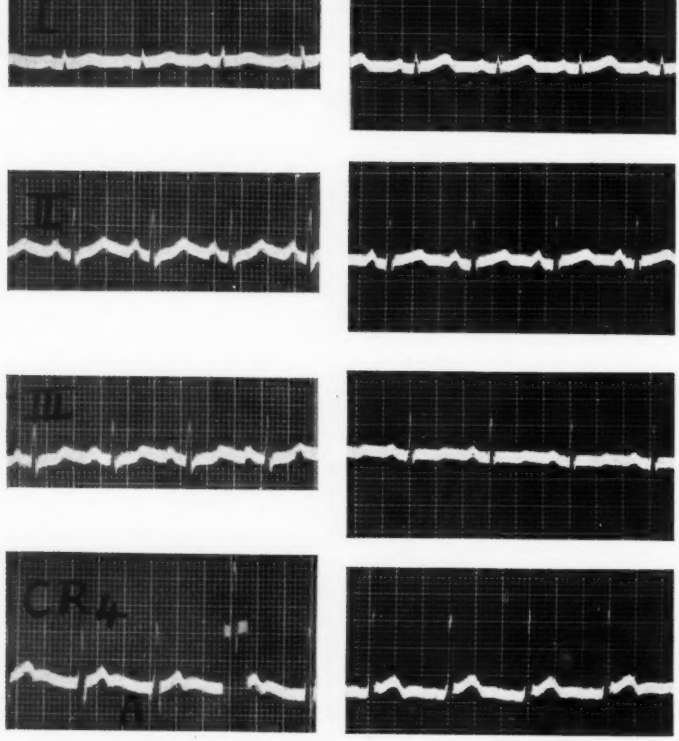

FIG. 6.—Electrocardiograms of Case 4. (A) 26/4/45. (B) 10/5/45.

Comment

The clinical story and physical findings in all four of these patients were essentially the same, varying only in degrees of severity. In no instance was there clinical evidence of vitamin deficiency. All were severely malnourished and dehydrated on admission and were suffering from diarrhœa. No patient had any symptoms or signs of cardiac or peripheral vascular disability, except Case 3, in whom a marked drop in blood pressure and tachycardia developed, accompanied by great weakness, but no other signs of shock. One patient had had moderate intermittent œdema prior to admission but showed none while in the hospital; another developed mild œdema after several days in hospital. In both instances this was considered to be nutritional in origin. In all four cases improvement after the first few days was steady. All showed rather small hearts by roentgenographic examination, and the cardiac findings on physical examination in each were normal. Most of them tended to run a raised temperature without any evidence of infection, which is an extremely common finding among the very undernourished patients. Of interest is the tetany which Case 2 developed without evidence of hypocalcæmia or alkalosis. Treatment other than that described in the case reports consisted of increasing amounts of food by mouth, including milk, eggs, and cereals with an addition of meat after some days. All patients were given 6 multi-vitamin capsules daily which provided a total daily intake of 15,000 U.S.P. units of vitamin A, 1200 U.S.P. units of vitamin D, 6·0 mg. of thiamin chloride, 9·0 mg. of riboflavin, 225 mg. of ascorbic acid, and 60 mg. of nicotinamide. In addition Cases 1 and 3 were given 30 mg. of thiamin and 50 mg. of nicotinamide intramuscularly daily for the first three or four days. (The parenteral nicotinamide was given in relatively small dosage because an adequate supply of this substance was not available at this time.) No digitalis or other specific cardiac medication was given.

Electrocardiographic Findings

The serial cardiograms on the four patients are shown in Fig. 1 to 6. The most striking feature is the unusual T waves. The duration of these deflections, as measured from the initial phase of the QRS complex to the final return to the isoelectric level, is greatly lengthened, and the final phase in all the early records is positive and usually well marked. This may represent a U wave, unusually large in the early tracings, which diminishes or disappears with improvement. The "bifid" T waves occurring in Cases 2 and 4 suggest this as well as the progressive changes in the fourth leads in the other two cases. However, in many of the records it is impossible to say that the entire complex is not T wave. For the sake of convenience and comparison the total duration of this interval has been expressed as the "Q–T interval," In two patients the P–R interval was slightly and inconstantly prolonged; in addition, in Case 1, a widening of the QRS complex occurred.

In all four patients the cardiograms had returned to normal within 14 to 21 days.

Cardiograms were taken in 10 additional severely malnourished soldiers. None had symptoms or signs of cardiovascular disability or of vitamin deficiency.

One showed a prolongation of the Q–T interval of 0·02 sec. above the maximum allowable for normal persons, and low amplitude of all T waves, with a return to normal within one week All other cardiograms were within normal limits.

Discussion

The electrocardiographic abnormalities exhibited by these four patients are unusual and tend to follow a common pattern, the most striking and constant feature being an unusually great prolongation of the Q–T interval or large U waves accompanying abnormal T waves. All of these patients were suffering from severe undernourishment and in addition were dehydrated, as judged from their obvious clinical condition and by the evidence of hæmodilution in Cases 1, 2 and 3, following treatment in the hospital (See Table 1).

None of these patients or any others among more than 400 personally observed showed any clinical evidence of vitamin deficiency. Observers who have studied very large numbers of persons who underwent chronic starvation under similar circumstances in Europe are agreed that clinical vitamin deficiencies are not common (Chapman, Meiklejohn, Pollack, personal communications, 1945).

Cardiographic abnormalities occur in beriberi, which is considered to be due to a lack of thiamin; Weiss and Wilkins (1937) found in a large series of patients studied that such abnormalities were present in 93 per cent of the cases. In 79 per cent the Q–T interval was prolonged beyond the maximum allowed by the Cheer-Li standard (0·38 sec.) and in 45 per cent it was greater than that permitted by the Shepley-Hallaran standard (0·43 sec.). Other changes noted consisted of lowering or inversion of T waves and minor changes in the QRS complexes.

Whether deficiencies in other vitamins lead to alterations in the electrocardiogram is not settled, but it was considered unlikely by Weiss and Wilkins. However, Rachmilewitz and Braun (1944) reported on two patients with severe diarrhœa who were " admitted in a state of severe deficiency." The first showed inversion of the T waves, and the second a well-marked prolongation of the Q–T interval. They attributed this to nicotinic acid deficiency since improvement occurred coincidentally with nicotinic acid administration. Feil (1936) previously had found the Q–T interval to be frequently prolonged in pellagra with a return to normal upon recovery. Usually this shortening of the Q–T interval, which occurred with improvement, ranged from 0·02 to 0·06 sec., but the maximum was 0·12 sec. In addition Feil described inversion of T waves and elevation or depression of the S–T interval as being not uncommon. In neither of these two articles is the possibility excluded that other deficiencies than lack of the pellagra-preventive vitamin complex may have been responsible for the cardiographic findings. Since clinical avitaminosis states are usually associated with multiple deficiencies, particularly as regards the B complex, it is difficult to assess the role that the lack of individual vitamins play in producing the cardiographic abnormalities.

The cardiographic pattern observed in the cases of the present study bears little resemblance to the characteristic changes reported previously in association with avitaminosis. As stated, these patients also had no clinical evidence of the cardiovascular manifestations of beriberi. There was no peripheral vasodilatation, no cardiac enlargement or heart failure, and no polyneuritis. Pellagrous lesions were absent. As Weiss and Wilkins have observed, since the tendency to develop avitaminosis varies directly with metabolic rate, clinical beriberi is not likely to develop in conditions of starvation and inanition.

Although a disturbance of the electrolyte balance of these undernourished patients undoubtedly occurred, it was impossible in this study to investigate this adequately. Hypocalcæmia characteristically produces a prolongation of the Q–T interval which is not uncommonly very marked in degree (Ashman, 1942, and Barker, Johnston, and Wilson, 1937). Other cardiographic changes do not usually develop with low serum calcium levels. None of the four patients studied had a reduction in blood serum calcium values below normal, although it is of interest that Case 2 developed clinical tetany. Since the plasma proteins were not increased it is unlikely that there was an abnormal reduction in the ionized calcium levels.

Pathological and experimental conditions causing abnormalities of the blood potassium produce cardiographic changes. When the potassium level in the blood is increased in man or animals experimentally by the administration of potassium salts (Winkler, *et al.*, 1938, and Chamberlain, *et al.*, 1939) or clinically in renal failure or Addison's disease (Thomson, 1939, and Keith, *et al.*, 1944) the cardiogram first shows an increased height of the T waves especially in the chest lead, with a narrow base and a " peaked " apex. With greater increases in the serum potassium level in experimental animals partial auriculo-ventricular block and intraventricular block occur. The T waves may also be lowered or inverted. The duration of electrical systole was slightly prolonged in three patients in uræmia with high serum potassium studied by Keith *et al.* (1944), but marked alterations in the Q–T intervals did not occur when this was produced experimentally (Chamberlain *et al.*, 1939).

Conversely, in a patient suffering from familial periodic paralysis, reported by Stewart, Smith, and Milhorat (1940), transient abnormalities occurred in the cardiogram when the serum potassium was reduced, consisting of prolonged P–R interval, widened QRS complex and prolongation of the Q–T interval with a depressed S–T interval and a lowering of T waves.

The cardiograms of the malnourished patients show little in common with the changes occurring with high serum potassium, and the similarities with the abnormalities found in the patient with low blood potassium, although slightly greater, are not at all marked. Whether

such similarity as exists is more than coincidental is merely conjectural since it was impossible to carry out blood potassium studies in these patients.

Post-mortem observations on patients dying of malnutrition (Meiklejohn, 1945, and Pollack, 1945) have revealed that the hearts are small and flabby with brownish pigmentation ; microscopically the muscle fibres show loss of striation. In those cases showing generalized œdema, particularly those who had received fluid and salt for some weeks before death, there was in addition evidence of inter- and intra-fibrillary œdema of the cardiac musculature.

Summary and Conclusions

Case reports are presented on four patients suffering from severe and prolonged malnutrition in whom electrocardiographic abnormalities were observed. These cardiographic changes consisted of a marked prolongation of the Q–T interval, or unusually well-marked but not persistent U waves, and less constantly, depression of the S–T segment, alterations in T waves, and increase in the P–R and QRS intervals.

Although the available evidence does not permit any certain conclusions to be drawn as to the causation of the cardiographic abnormalities occurring in malnourished persons, it is probable that they represent a composite picture due to prolonged protein and carbohydrate starvation and electrolyte imbalance. There was no evidence of a significant degree of anoxia of the cardiac muscle or of clinical avitaminosis. Vitamin deficiency, however, cannot be entirely ruled out as an ætiological factor in spite of the absence of clinical symptoms and signs. The fact that the cardiograms returned to normal within two to three weeks after the institution of an adequate therapeutic regime suggests that the changes are chiefly due to functional and not to structural causes.

We are indebted to the following for information supplied about the rarity of clinical signs of vitamin deficiency : Dr. A. P. Meiklejohn of U.N.R.R.A. from observations at the Belsen Concentration Camp, Lt.-Col. Herbert Pollack, A.U.S., from observations of liberated prisoners of war, and Dr. Carleton Chapman, U.S.P.H.S. and U.N.R.R.A., from observations in Greece and Jugoslavia : and to the two former for post-mortem observations on patients dying from malnutrition.

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THE EFFECT OF NITRITE AND EXERCISE ON THE INVERTED T WAVE

BY

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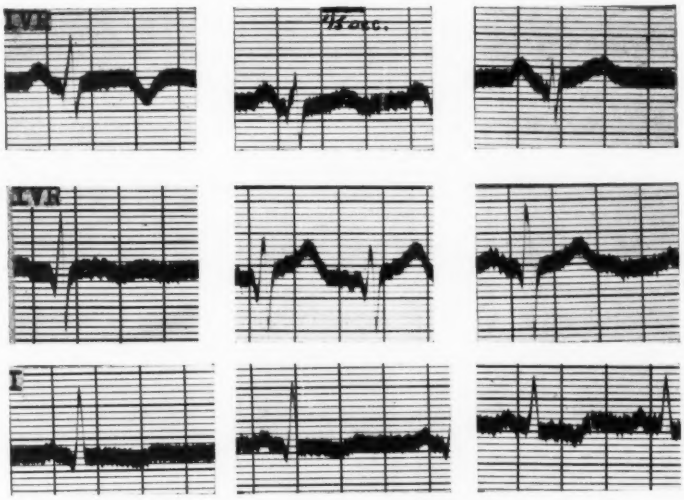
No unequivocal explanation has so far been found of the inverted T wave in the abnormal human electrocardiogram. It is likely that the deformed T wave associated with coronary disease is the outcome of cardiac ischaemia, but this does not appear to explain the mechanism of T-wave inversion in ventricular preponderance where a shift of the heart may play a part. The earlier papers dealing with temporary cardiographic changes in cardiac ischaemia and with the experimental evidence that nitrite increases the blood supply to the myocardium were reviewed by Evans and Hoyle (1933), who studied the effect of nitrite on the inverted T wave. In a series of 23 cases that showed deformity of the T in the form of flattening, diphasic change, or inversion, this component was wholly or partly corrected in 11 following the administration of the vasodilator. They concluded that elevation of the inverted T wave by nitrite in patients with angina pectoris was determined by the relief of myocardial ischaemia, and suggested that further observations might show that the fixed T wave and the one elevated by nitrite had a different significance, and that this might prove to be a measure of the collateral circulation around a damaged portion of heart muscle. Only nine of their cases, however, were of simple cardiac infarction without hypertension or aortic valvular disease, and in only three of these was the T wave corrected by nitrite. Exercising patients with coronary insufficiency will sometimes cause R–T depression or even inversion of the T wave; in others it may correct the deformity. Such changes were considered by Master, Friedman, and Dack (1942), as evidence of coronary abnormality. May (1939) observed that a lowering of the T wave, sometimes with S–T depression, as a result of the oxygen deficiency, gradually induced, is much more common in young athletic subjects than in older people. Levy, Alvan, and Bruenn (1938) agreed that oxygen want caused cardiographic alterations in healthy subjects as well as in patients with heart disease, but showed that the change was far greater when the coronary circulation was impaired. The effect of the administration of oxygen on the cardiogram of cyanosed patients was studied by Edson (1942), who found that the deformed T wave was not always corrected and especially in cases of recent coronary occlusion, while in some depression of the R–T segment or an increase in the degree of inversion of the T wave resulted. An understanding of T-wave changes in relation to myocardial nutrition is still far from complete. An explanation of the altered T wave of ventricular preponderance does not at first sight concern the relief of cardiac ischaemia. In practice, the similarity of the T I type of cardiac infarction and the inversion of T from hypertension or aortic valvular disease is a common problem in differential diagnosis. The chest lead CR_7 of Evans and Hunter (1943) may sometimes assist this differentiation, while the administration of potassium salts (Sharpey-Schafer, 1943) might help if it were a safe method. The following observations on the effects of nitrite and exercise on the inverted T wave were made to evaluate the help that such tests might afford in deciding this common clinical and cardiological problem.

The Investigation

Forty-five cases showing deformity of the T wave in their cardiograms were selected for the tests, and were divided into four groups; 16 cases of cardiac infarction (Group I); 13 of

hypertension without clinical evidence of coronary changes (Group II), 9 of cardiac infarction with hypertension (Group III), and 7 cases of aortic valvular disease (Group IV). The criteria adopted in the separation of Groups I and III were a resting blood pressure of 170 mm. systolic at the time of the test or recorded on a previous occasion, and cardiac enlargement on cardioscopy. In Group I, 10 cases of infarction were of the T I type (Parkinson and Bedford, 1928) and 6 of the T III type. Of those cases of infarction with hypertension (Group III), 3 showed cardiographic changes of the T I type and 6 of the T III type. The 20 cases of " left ventricular preponderance " who gave no history of pain that would have been interpreted as indicating coronary disease were made up of 10 cases of simple hypertension, 2 of malignant hypertension, 1 of chronic nephritis with hypertension (Group II), 1 of aortic incompetence, 1 of congenital sub-aortic stenosis, and 5 of aortic stenosis and incompetence (1 rheumatic, 2 atherosclerotic with hypertension, and 2 of syphilitic origin) (Group IV). Eleven of Group II showed changes in the T wave in lead I, as did all the cases in Group IV with the exception of



A B C

FIG. 1.—The effect of amyl nitrite and of exercise on the deformed T wave of three cases of cardiac infarction. (A) At rest. (B) After nitrite. (C) After exercise.

the patient with a congenital lesion, and in none of them was the inversion of T in IVR greater than in CR_7. At the start of this investigation other leads showing inversion of the T wave were studied, but in most the lead that showed the greatest deformity was selected whether it was lead I, lead II or lead IVR except that lead III was never used.

Nitrite was administered as follows. A capsule of amyl nitrite (5 minims) was broken in a gauze swab below the nose of the patient who was previously reassured as to the safety of the procedure. Four or five deep inhalations were taken. The selected lead was then recorded at half-minute intervals and the blood pressure noted regularly. After an interval, and often on another occasion, glyceryl trinitrate was chewed. Many patients received 3/100 grain, but as a rule a dose of 1/50 or 1/100 grain was taken. Several tracings were then recorded at intervals as well as blood pressure readings.

The exercise test took the form of bending repeatedly to touch the toes, or of raising and lowering the legs with the knees straight while the subject reclined on a couch with the electrodes in position. In order to avoid any influence of drugs, this test was always performed before the administration of the nitrites, and a sufficient interval was allowed between the different procedures for the pulse rate and for the tracing to return to their resting states. Exercise was continued for a few minutes until the patient became fatigued or breathless. Standard exercise tests, such as those devised by Master, Friedman, and Dack (1942) were

not attempted owing to the variable capacity of the subjects. The performance of this test on the couch minimized loss of time before recording the tracing, for Master and his co-workers stated that occasionally the cardiographic changes produced by exercise may disappear within one minute of the cessation of exertion.

Results

In Table I are analysed the effects of nitrite and exercise on the abnormal T wave. Nitrite corrected the deformity in six cases of Group I (37 per cent), in seven of Group II (54 per cent), in two of Group III (22 per cent), and in none of the seven cases of Group IV. In one case

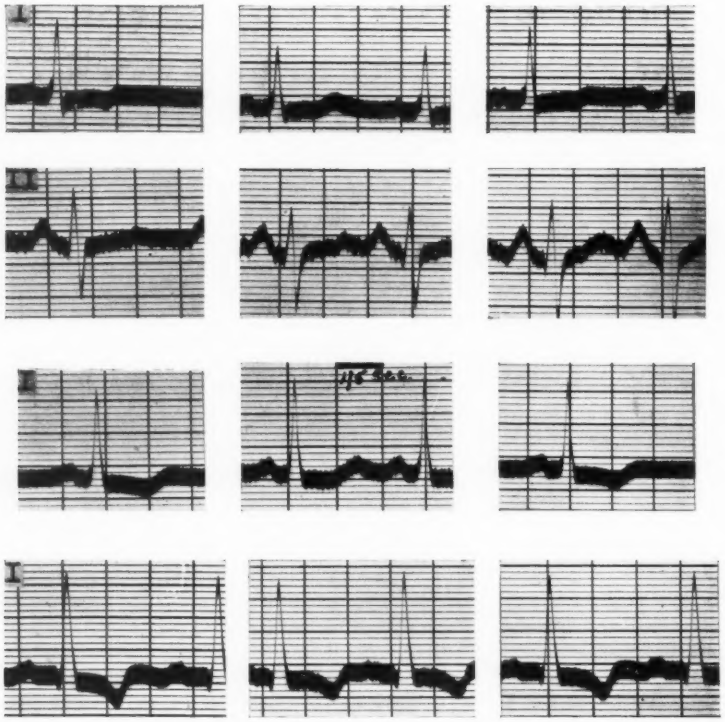


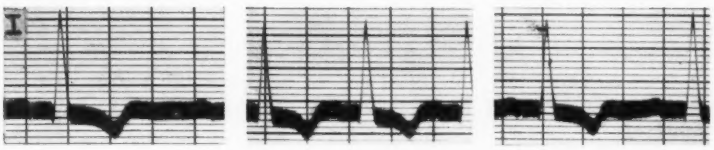
Fig. 2.—The effect of amyl nitrite and of exercise on the deformed T wave of four cases of hypertension. (A) At rest. (B) After nitrite. (C) After exercise.

in each of the first three groups the deformity of the T wave was accentuated. Elevation of this component resulted from exercise in 9 of 16 cases (56 per cent) of simple cardiac infarction (Group I), and in but 2 of the 13 cases (15 per cent) of hypertension without apparent coronary disease (Group II). Of these two, one was a case of benign hypertension, the other of malignant hypertension. Exercise did not alter the T wave in any case of aortic valvular disease (Group IV). No change resulted from nitrite or exercise in four cases of Group I (25 per cent), five of Group II (38 per cent), six of Group III (67 per cent), and seven of Group IV (100 per cent). Only among the cases of cardiac infarction without hypertension (Group I) were found instances of correction of the T wave from exercise but not from nitrite (25 per cent). On the other hand, in Group II five cases showed an elevation with nitrite but not with exercise whereas only one in Group I met with correction from nitrite alone.

TABLE I

THE EFFECTS OF NITRITE AND EXERCISE ON THE ABNORMAL T WAVE

Diagnosis	Effect of Nitrite			Effect of Exercise		
	Deformity corrected	No change	Deformity accentuated	Deformity corrected	No change	Deformity accentuated
Cardiac infarction (16)	6	9	1	9	6	1
Hypertension (13)	7	5	1	2	11	0
Cardiac infarction and hypertension (9)	2	6	1	1	7	1
Aortic valvular disease (7)	0	7	0	0	7	0



A B C

FIG. 3.—The effect of amyl nitrite and of exercise on the inverted T wave of a case of aortic stenosis with incompetence. (A) At rest. (B) After nitrite. (C) After exercise.

After glyceryl trinitrate, in only 5 of the total 45 cases was any change in the T wave noted, of which 2 received 3/100 gr.; 2, 1/50 gr.; and 1, 1/100 gr., whereas 18 of the cases showed some change after amyl nitrite. These cardiographic changes tended to occur three to five minutes after the patient started to chew the trinitrin and half to one minute after the inhalation of amyl nitrite. The fall of blood pressure after amyl nitrite was swifter, and was generally accompanied by flushing, palpitation, and occasionally faintness, and, although it lasted only one to two minutes, was more dramatic than that which resulted from chewing the tablet. A fall of 30 to 40 mm. pressure was common in cases with resting systolic pressures within normal limits. In subjects with hypertension a fall of 60 to 80 or even 100 mm. was recorded half to one minute after the inhalation, but the original pressure was reached a minute or so later. In few cases, usually those receiving the larger doses of glyceryl trinitrate, there was a corresponding fall of the systolic pressure recorded, and the effect took two to five minutes to develop. Peripheral vasodilatation was less marked, and with the exception of one instance of collapse in an elderly woman who received 3/100 gr., the subjective discomfort was far less. From these results there would appear to be no close association between the fall in blood pressure and the incidence of cardiographic change. Tachycardia was frequent within one minute of amyl nitrite administration, but only a slight increase of pulse rate was noted after trinitrin, presumably because of the factors mentioned, namely, less subjective disturbance and smaller and more gradual fall in blood pressure after the solid preparation. Judging from the results of amyl nitrite administration, there seemed no obvious association between tachycardia and correction of the T wave, as a high pulse rate was noted as frequently with no change in the T wave as in those with an alteration of the complex; there were instances where a case of cardiac infarction, showing correction of the T wave by exercise, failed to show any cardiographic change after nitrite, in spite of a higher heart rate; also, if tachycardia were responsible for this correction, a greater number of cases might be expected to show it after exercise in Group II. Although exercise in most cases caused an increase in the blood pressure (e.g. 150/120 to 195/140, 140/90 to 180/100, and 250/120 to 280/140) there seemed no relation between the degree or frequency of changes in the blood pressure and cardiographic records in any group.

Changes in the R–T segment were also noted, although only T wave alterations have been mentioned. In three cases of cardiac infarction R–T depression occurred with exercise but the T wave became taller, and in another the T wave was unchanged in spite of slight R–T depression.

Discussion

The present results with nitrite are comparable with those obtained by Evans and Hoyle (1933); 18 of a total of 45 cases showed a change in the T wave after administration of the vasodilator, whereas the figures of the previous observers were 11 of 23 cases. In the present series, in 6 of the 16 cases of cardiac infarction in Group I the deformity was corrected whereas the comparable figures in the 1933 publication were 3 out of 9 cases. Turning to Group II one finds a more frequent change in the T wave after amyl nitrite in cases of hypertension without apparent coronary lesions than in those with infarction. In 7 of the 13 cases the T wave was corrected in Group II (54 per cent) compared with 6 of 16 cases in Group I (37 per cent). If the cases of left ventricular preponderance including hypertension and aortic valvular disease (Groups II and IV) were not separated, the figures for correction by nitrite would be closer (35 per cent for Group II + Group IV). The effect of nitrite, therefore, cannot serve usefully in differentiating the cardiogram of cardiac infarction from that of left ventricular preponderance. The elucidation of cardiographic changes of the T I type occurring with hypertension and coronary pain must depend as yet on the history and on the clinical findings, while some help may be obtained from the chest lead CR_7 of Evans and Hunter.

If the relief of myocardial ischaemia is the only factor determining correction of the deformed T wave of infarction, difficulty arises in the explanation of similar cardiographic changes after exercise. An increase in the general circulation rate will lead to a greater coronary circulation rate unless the vessels are completely occluded (Peel, 1943). It is a well-known fact that patients with angina are sometimes hindered by pain at the start of a walk, but after a short distance may gain their " second wind " and complete the journey without further interruption. Anginal pain, however, accompanied the elevation of the T wave in four cases of this series, which fact does not conform to the theory of improved coronary flow with a certain amount of exertion. There is no doubt that both amyl nitrite and glyceryl trinitrate cause dilation of the coronary arteries and that these drugs will prevent the pain and also the associated R–T depression or T wave inversion, produced by exercise in some patients with angina. It is difficult to explain why glyceryl trinitrate, generally considered as powerful an antispasmodic as amyl nitrite, if not so prompt in action, does not produce comparable correction of the inverted T wave. The possibility that tachycardia induced by the volatile drug and by exercise, might influence this cardiographic alteration has already been discussed with cautious disbelief. These conclusions are in agreement with those of Evans and Hoyle.

As regards the cardiogram of left ventricular preponderance, the characteristic changes, including T-wave inversion, are presumed to depend on the anatomical configuration of the cardiac chambers in relation to each other and to the chest as a whole, and not on the condition of the heart muscle (Master, 1942). Myocardial ischaemia is not considered to be a factor. One may next look to a change in posture of the heart to explain the correction by nitrite of the hypertensive T wave deformity. A recent claim by Goldberger (1945), that such changes are similar, if not identical, with those produced by deep inspiration, requires consideration. Goldberger associates this correction with rotation of the heart and suggests that, although other factors may take part, this same mechanism underlies the effects of nitrite. The heart, which according to Scherf and Zdansky (1929) decreases in size following inhalation of this drug, is assumed by Goldberger to lie more vertically, and thus rotation would occur as in the assumption of the upright posture with deep inspiration. Hyperventilation was also often observed after amyl nitrite inhalation. From a comparison of the changes induced in the inverted T wave by deep inspiration in the upright position with those due to amyl nitrite, it would appear that the alteration of cardiac posture must play little if any part in the effects of the vasodilator (Fig. 4). Four cases of infarction and seven of hypertension were tested for such effects. When the selected lead (lead I in ten cases, lead II in one case) had been recorded with the patient lying flat, it was repeated in the upright posture during deep inspiration. Amyl nitrite was subsequently administered with the subject in the reclining position so that the effect of the vasodilator on the cardiogram could be compared with that of cardiac tilt. Only in one of the four cases of cardiac infarction and in two of the seven cases of hypertension so tested, did postural change with depression of the diaphragm cause a very slight correction of the deformed T wave. The effect of amyl nitrite on the size of the heart needs to be confirmed, but my results from varying the posture of patients with deformity of the T wave in

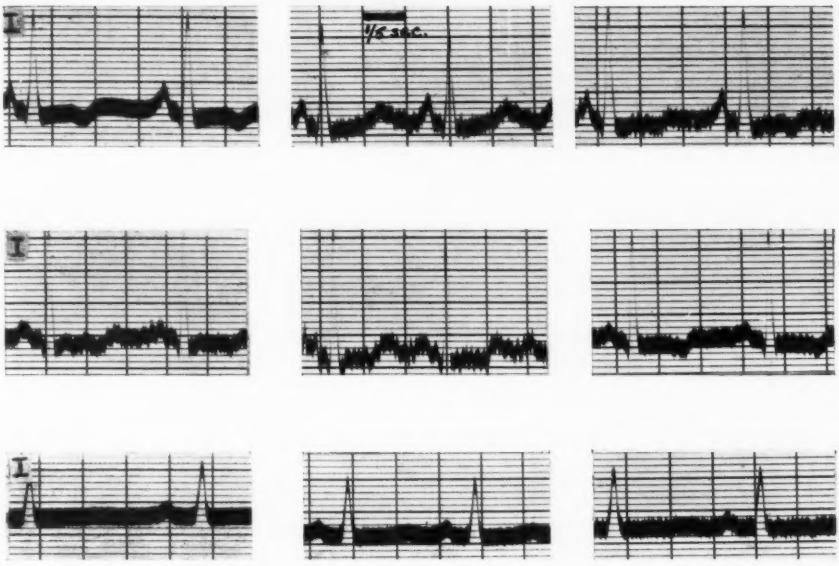


FIG. 4.—The effect of amyl nitrite and of deep inspiration in the upright posture on the deformed T wave of two cases of hypertension and one of anterior cardiac infarction. (A) Supine. (B) After nitrite. (C) Upright inspiration.

the cardiogram are not in agreement with those of Goldberger. Meanwhile, no satisfactory explanation is forthcoming for the correction by nitrite of the inverted T wave of hypertension.

SUMMARY AND CONCLUSIONS

The effect of nitrite and of exercise on the inverted or depressed T wave of the cardiogram was studied in 45 patients. These were divided into four groups. Group I consisted of 16 cases of cardiac infarction without hypertension, Group II of 13 cases of hypertension without clinical evidence of coronary disease, Group III of 9 cases of infarction with hypertension, and Group IV of 7 cases of aortic valvular disease.

Inhalation of amyl nitrite will often correct the inverted T wave of the cardiogram in cardiac infarction (6 of 16 cases). As often it will correct the deformed T wave of hypertension (7 of 13 cases) but no such changes resulted in any of the 7 cases of aortic valvular disease.

Exercise will give similar results in that it righted the deformed T wave in 9 of 16 patient with cardiac infarction, and in 2 of the 13 with hypertension; in none of the 7 with aortic valvular disease was there any change.

In 11 cases the T wave of the cardiogram taken when the patient was in the upright posture, with the diaphragm depressed by deep inspiration, was seldom different from the tracing in the supine posture on quiet respiration.

It is not even certain that the corrected T wave from nitrite inhalation and exercise is brought about by the relief of myocardial ischaemia since the deformed T wave of hypertension responds in the same way. Tachycardia and variation in blood pressure and of posture seem to play no part in such correction.

The tests of amyl nitrite inhalation, exercise, and change of posture will not assist in differentiating the cardiographic pattern of cardiac infarction from that of hypertension.

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AURICULAR PREMATURE SYSTOLES: THE DURATION OF THE ELECTRICAL SYSTOLE

BY

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In a recent electrocardiographic investigation (Berliner and Lewithin, 1945) the aberration of the ventricular complex of auricular premature systoles (*APS*)* was studied. Variations in amplitude, duration, direction, and configuration were found and described in detail. In the course of that investigation, a new feature of the *APS*, shortening of the electrical systole (Q–T interval), was discovered. This subject has since been studied by careful measurements which are reported in the present paper.

Material and Method

We used 100 electrocardiograms of different patients in this study, selected from the records of over 250 patients exhibiting *APS*. The selection was made on the basis of technical qualities of the tracings. We chose only clear records in which the exact end-points of the T waves were easily discernible. Tracings blurred by muscle tremor or technical defects were eliminated; as were such perfect records in which low amplitude of the T waves made accurate measurement of the Q–T interval impossible; and also all those records in which the *APS* were found to occur at the beginning of a tracing or at its very end (with the exception of Fig. 2A). Records with inverted T waves were purposely included.

Of the four leads available in practically all cases, we selected that lead in which the end-points of the T waves were most distinct, and analyzed one *APS* of that lead. The degree of prematurity of this *APS* and the degree of its aberration were determined first, and for this purpose the criteria established in the previous study were again used. Measurements were then made on five successive heart beats, the two beats preceding the *APS*, the *APS* itself, and the two beats following it. All measurements were made with the aid of a magnifying glass. The duration of QRS and RS–T † was measured in each of the five beats. The Q–T intervals were then obtained by adding up the values for QRS and RS–T. In the normal beat just preceding the *APS*, however, RS–T and Q–T could usually not be measured because the P wave of the *APS* was superimposed on its T wave. That was the reason why the beat preceding it was also measured and was chosen as *the* normal for purposes of comparison. QRS, RS–T, and Q–T of the *APS* were compared with the respective intervals of the normal beat and the post-extrasystolic beat. Examples are given in the legend to Fig. 1.

Results

QRS duration and Q–T interval. In 47 of our 100 *APS*, the duration of QRS did not differ from that of the normal beats or the difference was too minute for measurement. In 23, QRS duration was shortened; this shortening never exceeded 0·02 second. In 30 the QRS complexes were prolonged. The prolongation was marked (0·02 second or more) in 15 of these. Marked prolongation was usually associated with other features of aberration, viz.

* *APS* will be used as an abbreviation for auricular premature systole(s) throughout this paper.

† By RS–T interval we mean the interval beginning at the RS–T junction and ending at the end of the T wave.

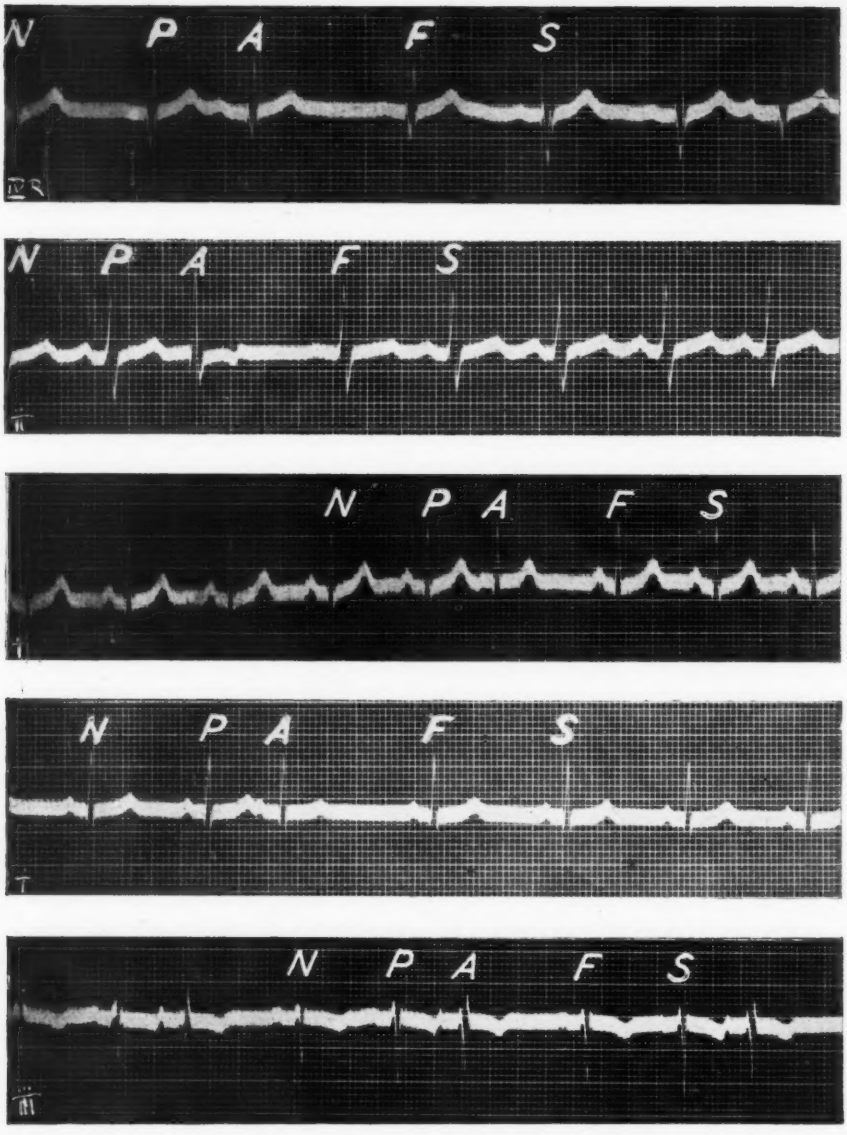

FIG. 1.—Shortening of the electrical systole in auricular premature systoles (*APS*)—five typical examples. QRS duration essentially unchanged, RS–T duration (from the RS–T junction to the end of T) shortened. N, normal beat; P, beat preceding the *APS*; A, *APS*; F, beat following the *APS*; S, subsequent beat. Measurements in seconds:

(A)	QRS	RS–T	Q–T
N	0·075	0·275	0·350
P	0·075	0·275	0·350
A	0·075	0·260	0·335
F	0·080	0·285	0·365
S	0·080	0·280	0·360

(B)	QRS	RS–T	Q–T
N	cut off	0·28	×
P	0·085	×	×
A	0·085	0·26	0·345
F	0·080	0·29	0·370
S	0·095	0·28	0·375

(C)	QRS	RS–T	Q–T
N	0·07	0·30	0·37
P	0·075	×	×
A	0·07	0·29	0·36
F	0·07	0·32	0·39
S	0·07	0·30	0·37

(D)	QRS	RS–T	Q–T
N	0·07	0·31	0·38
P	0·065	×	×
A	0·07	0·28	0·35
F	0·07	0·32	0·39
S	0·065	0·32	0·385

(E)	QRS	RS–T	Q–T
N	0·07	0·32	0·39
P	0·07	×	×
A	0·07	0·25	0·32
F	0·07	0·31	0·38
S	0·07	×	×

changes in amplitude, configuration, or direction. When we measured the duration of RS–T in the 15 *APS* which showed marked prolongation of QRS, we often found marked shortening of RS–T. So great was the shortening of RS–T in 9 of these 15 cases, that it " compensated " for the increase in QRS duration, making the total Q–T interval of the *APS* equal to the Q–T interval of the normal beats or even shorter. An example will illustrate this point (Fig. 3A, compare A with N).

QRS of *APS* (A) prolonged by	0·05 second
RS–T of *APS* (A) shortened by	0·06 second
Q–T interval of *APS* (A) shortened by	0·01 second

Our measurements of the QRS duration of *APS* may be summed up by the statement that changes in QRS duration did not significantly affect the Q–T interval of the *APS*.

Measurements of RS–T. The Q–T interval of an *APS* is usually shortened. This shortening occurs in the RS–T interval. When the RS–T interval of the *APS* was compared with that of the normal beat (N), it was found shortened in 82 per cent of the cases (Fig. 1). In 12 per cent there was no difference in RS–T duration, and in only 6 per cent was there a slight prolongation (Fig. 2).

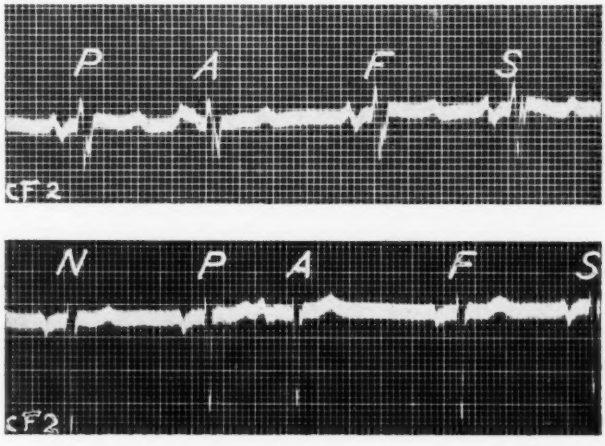

FIG. 2.—Slight lengthening of the electrical systole in auricular premature systoles (*APS*)—two examples of an unusual condition. QRS duration essentially unchanged, RS–T duration (from the RS–T junction to the end of T) lengthened. N, normal beat; P, beat preceding the *APS*; A, *APS*; F, beat following the *APS*; S, subsequent beat. Measurements in seconds.

(A)

	QRS	RS–T	Q–T
N		cut off	
P	0·095	0·325	0·42
A	0·09	0·33	0·42
F	0·095	0·33	0·425
S	0·10	0·32	0·42

(B)

	QRS	RS–T	Q–T
N	0·07	0·26	0·33
P	0·08	0·26	0·34
A	0·08	0·27	0·35
F	0·07	0·29	0·36
S		cut off	

We were unable to discover what causes the shortening of RS–T in the *APS*. Various possible factors were investigated. The effect of T-wave inversion was easily ruled out. Leads in which all T waves or only the T waves of the *APS* were inverted showed no more shortening than leads in which they were upright. We then studied the effect which the degree of prematurity of an *APS* might have on its RS–T duration. For this purpose, we compared the RS–T intervals of early and late *APS*. Our series included 15 early *APS*; their P waves were superimposed on the ascending limb of the preceding T wave (" location 4 " of the previous paper). Our series also included 23 late *APS* the P waves of which did not touch the preceding T waves (" location 1 " of the previous paper). Shortening of RS–T was no more marked in the early *APS* than in the late ones, and the frequency of RS–T shortening was the same in

both groups (Table I). We concluded that the degree of prematurity of an *APS* has no influence on the duration of its RS–T interval.

TABLE I.—Comparison of Early and Late Auricular Premature Systoles (*APS*)

	Number over of cases	RS–T interval shorter than normal	RS–T interval identical with normal beats	RS–T interval longer than normal	Shortening of RS–T varied
Early *APS* (location 4)	15	13	0	2	From 0·01 to 0·07 second.
Late *APS* (location 1)	23	19	3	1	From 0·005 to 0·06 second.

Another possible factor investigated by us was the degree of aberration, but it too was ruled out. *APS* with aberration showed no more shortening of RS–T than *APS* without any aberration. One group of markedly aberrant *APS*, however, formed an exception, viz. *APS* with marked prolongation of their QRS complexes. As mentioned above, in most of these *APS* (9 out of 15 cases) prolongation of QRS was accompanied by an extra marked shortening of RS–T. At times, this shortening of RS–T was so marked that it overbalanced the prolongation of QRS; the duration of Q–T was then shorter than that of the normal beats (Fig. 3A). The highest degrees of RS–T shortening, by as much as 0·06 and 0·07 sec., occurred in

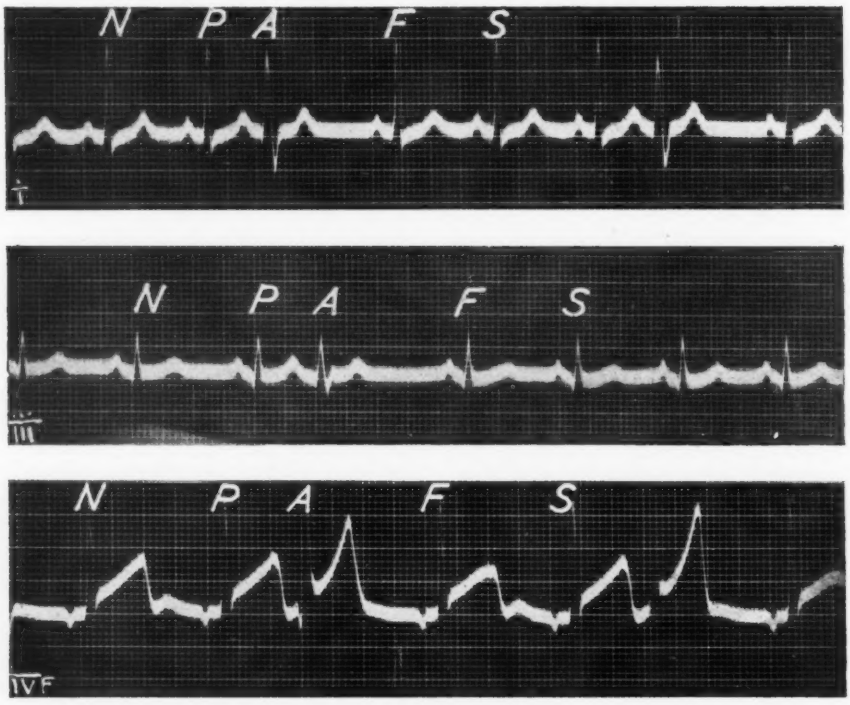

Fig. 3.—Auricular premature systoles (*APS*) showing increased QRS duration but markedly decreased RS–T duration—three examples. N, normal beat; P, beat preceding the *APS*; A, *APS*; F, beat following the *APS*; S, subsequent beat. Measurements in seconds.

(A)	QRS	RS–T	Q–T
N	0·08	0·31	0·39
P	0·08	×	×
A	0·13	0·25	0·38
F	0·09	0·31	0·40
S	0·08	0·31	0·39

(B)	QRS	RS–T	Q–T
N	0·06	0·28	0·34
P	0·07	×	×
A	0·12	0·23	0·35
F	0·07	0·29	0·36
S	0·07	0·29	0·36

(C)	QRS	RS–T	Q–T
N	0·065	0·37	0·435
P	0·07	×	×
A	0·10	0·34	0·44
F	0·07	0·38	0·45
S	0·07	×	×

such *APS* with markedly prolonged QRS complexes. This may be more than a coincidence; in fact, it suggests a possible interdependence of QRS and RS–T. There were, on the other hand, 3 cases in which such "compensation" did not take place; both the QRS and the RS–T intervals were prolonged, resulting in marked prolongation of Q–T, up to 0·12 sec. (Fig. 4A and Table II).

TABLE II

AURICULAR PREMATURE SYSTOLES (*APS*) WITH MARKED INCREASE IN QRS DURATION. (Measurements in seconds.)

	QRS duration increased by	RS–T duration shortened by	RS–T duration lengthened by	Resulting Q–T compared to normal	Illustrated in
1	0·02	0·04	—	−0·02	
2	0·02	0·04	—	−0·02	
3	0·02	0·02	—	identical	
4	0·02	0·01	—	+0·01	
5	0·03	0·03	—	identical	Fig. 3C
6	0·03	0·03	—	identical	
7	0·03	0·02	—	+0·01	
8	0·03	0·01	—	+0·02	
9	0·03	—	0·01	+0·04	
10	0·04	0·04	—	identical	
11	0·04	—	0·035	+0·075	Fig. 4A
12	0·04	—	0·08	+0·12	Fig. 4B
13	0·05	0·06	—	−0·01	Fig. 3A
14	0·05	0·05	—	identical	
15	0·06	0·05	—	+0·01	Fig. 3B

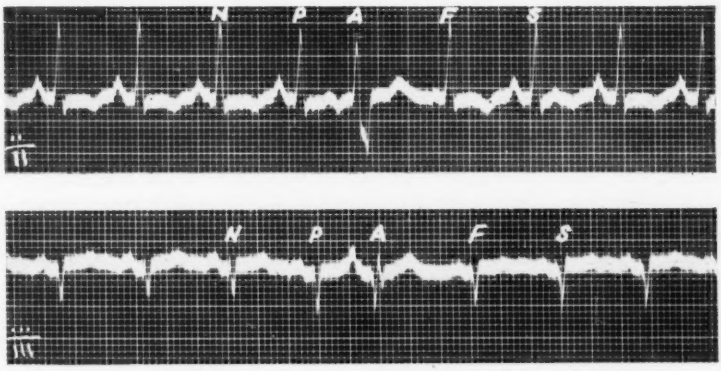

FIG. 4.—Auricular premature systoles (*APS*) showing increased duration of both QRS and RS–T—two examples. N, normal beat; P, beat preceding the *APS*; A, *APS*; F, beat following the *APS*; S, subsequent beat. Measurements in seconds.

(A)

	QRS	RS–T	Q–T
N	0·08	0·24	0·32
P	0·085	×	×
A	0·12	0·32	0·44
F	0·08	0·26	0·34
S	0·08	0·25	0·33

(B)

	QRS	RS–T	Q–T
N	0·06	0·225	0·285
P	0·055	×	×
A	0·10	0·26	0·36
F	0·06	0·23	0·29
S	0·07	0·22	0·29

Comparison of APS *with the following beat.* The beat following an *APS* has a prolonged RS–T interval. When we compared the post-extrasystolic beat with the *APS*, the RS–T prolongation of the former was a practically constant finding. But even when we compared the post-extrasystolic beat with the normal beat N, prolongation of RS–T was found in a high percentage of cases (Table III). The prolongation usually amounted to 0·01 to 0·02 sec., but greater prolongation, of 0·06, 0·07, and even 0·08 sec. occurred occasionally. The effect of

the pause was obvious. In general, the longer the pause after an *APS*, the greater was the prolongation of the RS–T interval of the following beat; but this relationship was by no means consistent, and actual shortening of the RS–T interval of the following beat occasionally occurred, even after a long pause.

TABLE III

COMPARISON OF POST-EXTRASYSTOLIC BEAT (F) WITH AURICULAR PREMATURE SYSTOLE (*APS*) AND WITH NORMAL BEAT (N)

	RS–T longer (per cent)	RS–T identical (per cent)	RS–T shorter (per cent)
F compared with *APS* ..	97	1	2
F compared with N	68	22	10

COMMENT

Our investigation has established two facts: The RS–T interval (and thereby the Q–T interval) of an auricular premature systole is shortened, that of the post-extrasystolic beat is lengthened. Shortening of the electrical systole is a feature of auricular premature systoles not heretofore known, and its significance is not yet understood. Observations on the Q–T interval of normal beats were published by us (Berliner, 1931). Since then, knowledge of this subject has not materially increased. Varied factors, e.g. blood calcium level and digitalis, are known to influence the Q–T interval of normal beats but the determining factor unquestionably is the heart rate. The Q–T interval is shorter for faster rates and longer for slower rates. The relationship of heart rate and Q–T interval is expressed by Bazett's formula (1920)

$$Q\text{–}T = K \cdot \sqrt{\text{cycle length}},$$

the constant K being 0·37 for men and 0·40 for women. This formula or any of its variants obviously applies to beats occurring in regular rhythm and cannot be used to predict the Q–T interval of premature beats. It was, therefore, not employed in the present study. Rate or cycle length may, however, still be found to have an influence on the Q–T interval of premature beats and post-extrasystolic beats. Following the post-extrasystolic pause we found the Q–T interval lengthened. There, at least, the influence of cycle length appears very probable.

We were unable to find out what causes the variations of RS–T duration discovered by us. We may, however, have a clue in the contrast between shortened RS–T in the *APS* and lengthened RS–T in the post-extrasystolic beats. In a separate investigation of ventricular premature systoles, which will be reported later, we found exactly the same conditions; the RS–T intervals of ventricular premature beats are also shorter than those of normal beats (irrespective of the large size of the T waves), and the RS–T intervals of the post-extrasystolic beats are longer. It seems most likely to us that the shortening of RS–T in all premature systoles is caused by their prematurity. Prematurity results in incomplete diastolic filling of the ventricles, and this may be reflected in a shorter duration of RS–T. The post-extrasystolic pause, on the other hand, leads to greater diastolic filling of the ventricles, and this may give rise to an increased RS–T duration. Should this assumption be proved correct, we might be brought nearer to the solution of a basic electrocardiographic problem. The significance of RS–T interval variations in *normal* beats has always been obscure. It might then be found that they too are caused by changes in the diastolic filling of the ventricles.

In conclusion, a remark about measurements of Q–T intervals in general may be in order. Our findings clearly show that the QRS and RS–T intervals vary separately and perhaps independently. They should, therefore, be studied separately. Albers and Bedbur (1941) did that and found that the duration of QRS depends on the heart rate, the duration of RS–T on the heart rate, the age of the patient, and the degree of axis deviation. It was mentioned before that we repeatedly found prolongation of QRS associated with marked shortening of RS–T; the resulting Q–T interval was normal or nearly normal (Fig. 3). Simple measurements of Q–T in such cases would not have revealed the marked shortening of RS–T. Our

experience, therefore, convinces us that measurements of Q–T alone are insufficient and should be replaced by separate measurements of QRS and RS–T.

Summary and Conclusions

The duration of QRS and RS–T of 100 auricular premature systoles (*APS*) was measured and two facts were established: (1) the RS–T interval of an *APS* is usually shorter than that of normal beats, and (2) the RS–T interval of the post-extrasystolic beat is lengthened.

The greatest degrees of shortening of RS–T were found in *APS* with marked widening of their QRS complexes. As a result, the Q–T interval of these *APS* was no longer than that of the normal beats.

QRS and RS–T intervals of *APS* vary independently and should be studied separately. Simple measurements of Q–T intervals are insufficient.

Shortening of RS–T in *APS* is probably caused by the incomplete diastolic filling of the ventricles resulting from prematurity, while lengthening of RS–T in post-extrasystolic beats is probably caused by greater diastolic filling.

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PULMONARY VASCULAR SCLEROSIS WITH RIGHT VENTRICULAR FAILURE

BY

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The following is an account of a patient with pulmonary vascular sclerosis who died of right ventricular failure within four months of the appearance of the first symptom of ill health.

A navvy charge hand, aged 34, was admitted to Addenbrooke's Hospital on November 6, 1942. In August 1942 he noticed that some of his teeth were very loose and tended to bleed easily, and shortly after this that he was breathless on exertion. Until then he had always been fit with no cough or breathlessness. In early October he went to the dentist, and twelve teeth were extracted under general anæsthesia. Following these extractions breathlessness on exertion gradually increased so that when he was admitted to hospital he could walk up six steps only with difficulty. A week before admission he had also noticed slight swelling of his left leg, occasional palpitation, and some upper abdominal pain and flatulence after food. His appetite remained good and his weight constant. His work had not been physically very strenuous but his hours had been long—from eight in the morning sometimes until midnight. As this was seven miles from home he used to cycle to and fro. He often worked a seven-day week.

In the past he had had no serious illnesses, no rheumatism, nor rheumatic fever, nor other condition that might predispose to cardiac trouble. He had been accustomed to smoke up to 50 cigarettes a day and drank a moderate amount of beer but no spirits. His family history was healthy and did not suggest any tendency to arteriosclerosis or cardiac disease. His mother and father and brothers and sisters were all alive and well.

On admission he was very breathless and slightly cyanosed. The pulse was regular—rate 100. Blood pressure 140/90, respiratory rate 20, temperature normal. A teleradiogram showed that the heart was enlarged (15·3 cm. in the transverse diameter) with marked bulging of the pulmonary artery (Fig. 1). The cardiogram showed right axis deviation with inversion of T II and T III (Fig. 2). The heart sounds were poor in quality with gallop rhythm and the pulmonary second sound was accentuated. There were no murmurs, clubbing of the fingers, venous pulsation, nor œdema, and no evidence of arteriosclerosis in the radial, brachial, or retinal arteries. The respiratory movements were good and there were no signs of chronic bronchitis or emphysema; a few crepitations were audible at the right base.

The liver appeared congested, the edge being palpable two inches below the costal margin. There was no abdominal tenderness and no evidence of ascites. The remaining teeth appeared healthy and the gums had healed well following extraction. The urine contained a trace of albumin, but was otherwise normal.

Blood count showed 5·6 million red corpuscles with hæmoglobin 112 per cent and 12,800 leucocytes with a normal differential count. Blood culture was sterile and the Wasserman reaction of the blood was negative. Blood urea 37 mg. per 100 c.c. Blood sedimentation rate on two occasions 1 and 4 mm. per hour respectively.

Progress. In spite of treatment by rest and full digitilization, progress was steadily downhill from the day of admission until death on December 2, 1942. During this period there was practically no change in either the pulse rate or the respiratory rate. Breathlessness and distress on the slightest exertion became progressively more marked and cyanosis steadily increased.

Post-mortem Examination

Congestion of the lungs, the lower lobes being tough and slightly nodular in consistency and the cut surface of the anterior borders yellowish-grey in colour, with many small rusty-red patches. Considerable emphysema of anterior borders only, without noticeable distention of the lung or formation of bullæ. One small fragment of ante-mortem thrombus in a small pulmonary artery in the right lower lobe, the area supplied by this vessel being hyperæmic but not infarcted. Unusually conspicuous blood vessels everywhere on the cut surfaces of the lungs. Conspicuous atheroma of main pulmonary artery and all its larger branches. Pulmonary veins normal. Only slight atheroma of aorta and its branches, almost none of coronary arteries. Slight excess (about 50 c.c.) of clear yellow fluid in

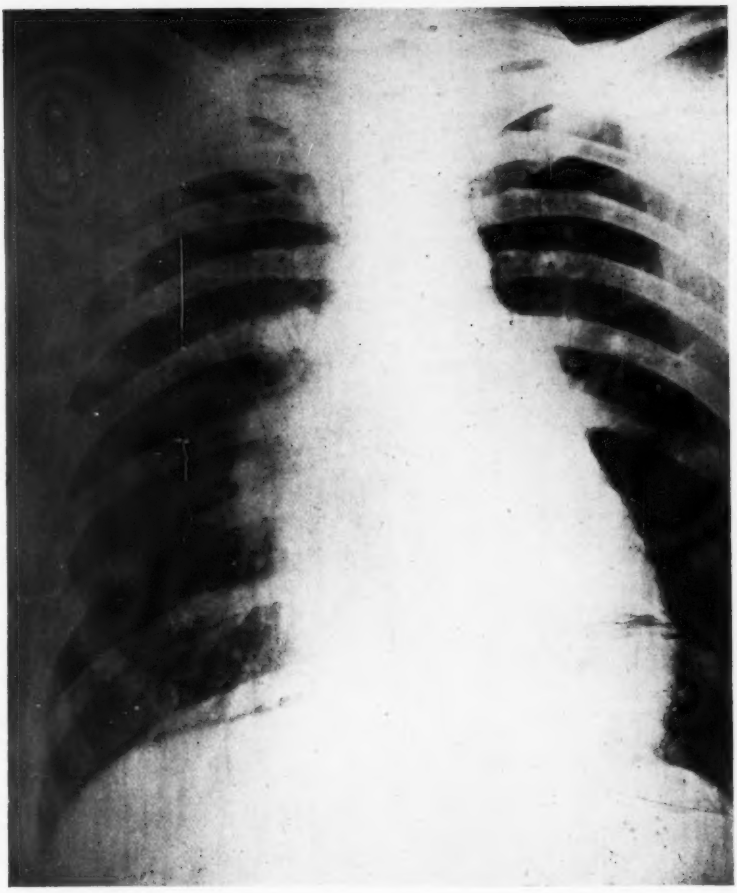

FIG. 1.—Radiogram showing large pulmonary artery.

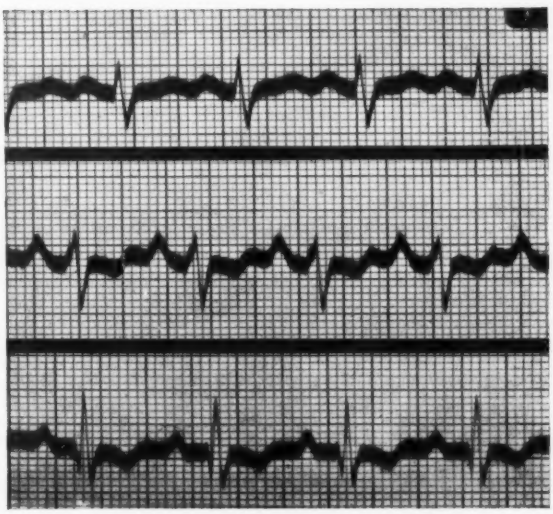

FIG. 2.—Cardiogram showing right axis deviation.

pericardium. Great dilatation of right side of heart, the cavity of both auricle and ventricle being about double the normal size. Considerable hypertrophy of right ventricle, its wall being stiff like a piece of leather. No hypertrophy or dilatation of left auricle or ventricle. Thickness of right ventricle 0·8 cm. Thickness of left ventricle 1·4 cm. The degree of hypertrophy was considerably more than is represented by these figures because of the great dilatation of the right ventricle. Brownish red, rather opaque myocardium; with frequent small greyish patches (0·1–0·2 cm. diameter) in the wall of left ventricle suggesting slight fibrosis; heart valves normal. Ante-mortem thrombus in right auricular appendage and also adhering to the wall of the right auricle at the site of the foramen ovale, which was patent (0·2 cm. diameter) but valvular. No clot projecting through the foramen into the left auricle nor any ante-mortem thrombus anywhere in the left side of the heart. Considerably enlarged hyperæmic and anthrocotic bronchial lymph glands, probably acutely inflamed, at hilum of left lung and at bifurcation of trachea. No abnormality of other lymph glands. Dilated stomach. Congestion and mucous catarrh of intestines. Chronic venous congestion of liver with œdematous connective tissue around the normal gall-bladder.

Small effusions of clear yellow fluid in each pleural cavity and in peritoneum (about 115 c.c. in each). Moderately enlarged firm " chronic heart failure " spleen. Congestion and cloudy swelling of kidneys. Two recent infarcts and an adenoma (0·4 cm. diameter) in left kidney. Bladder, prostate, and urethra normal, also testes and epididymis. Suprarenals, pancreas, thyroid, and pituitary normal; thymus for the most part replaced by fat. Normal brain. Middle ears clear. Pyorrhœa around bases of remaining teeth; teeth otherwise in fair condition; gums healed at sites of absent teeth. No clubbing of fingers; no œdema. Considerable cyanosis. Well-developed, well-nourished man.

Weight of Organs. Heart 455 g., left lung 610 g., right lung 710 g., liver 2080 g., spleen 280 g., right kidney 130 g., left kidney 155 g.

Microscopical Examinations

The Lungs. Six sections from different parts of the lungs show extensive disintegration of the alveolar walls, although only the anterior borders of the lungs are frankly emphysematous. In some areas—usually where alveoli are intact—capillaries are greatly engorged: elsewhere the tattered alveolar walls appear almost bloodless (Fig. 3). The contrast between the sharply defined patches of capillary engorgement and the surrounding zones in which it is difficult to distinguish any capillaries

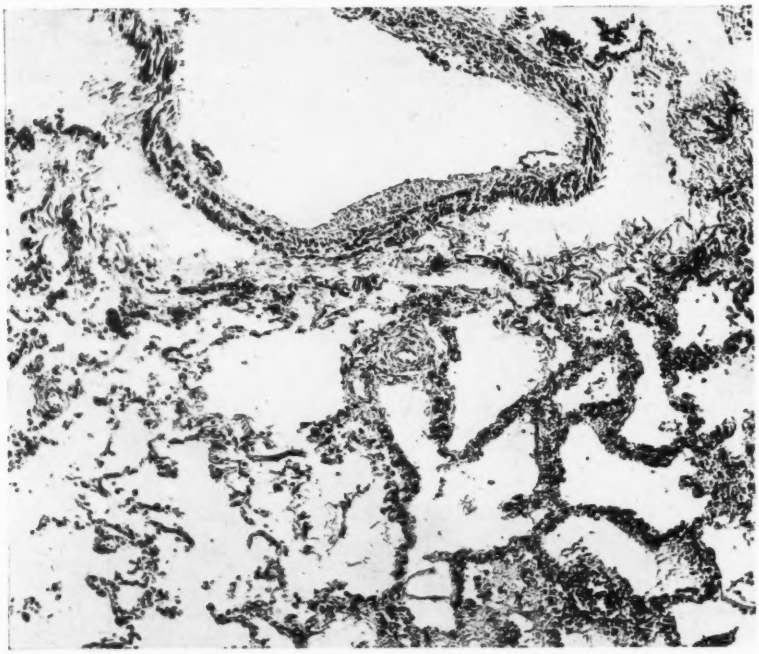

Fig. 3.—At the top, a small muscular artery with conspicuous intimal thickening; arteriole with greatly thickened wall in centre; area of capillary engorgement with preservation of alveolar pattern at bottom right; area of alveolar disintegration with few visible capillaries at bottom left.
Goldner's modification of Masson's stain. Magnification ×88.

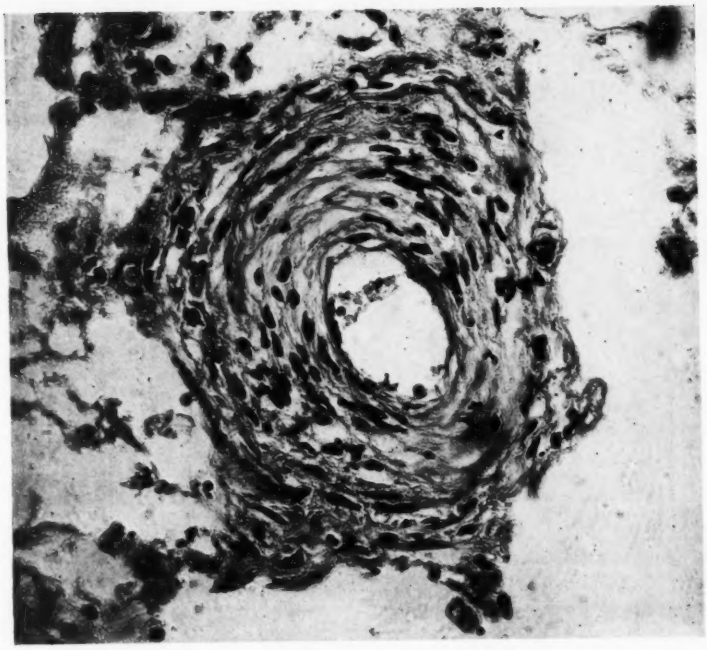

FIG. 4.—An arteriole more highly magnified, showing the characteristic lesion. Ehrlich's hæmatoxylin and eosin. Magnification ×390.

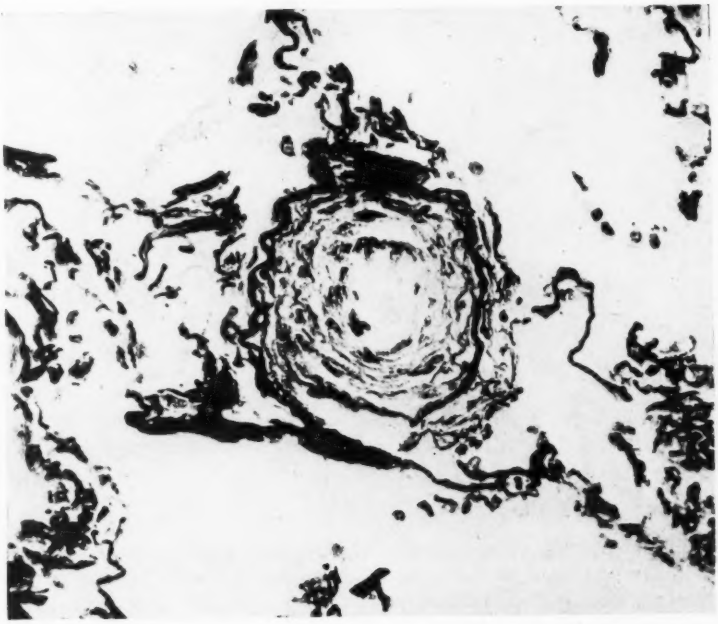

FIG. 5.—Another arteriole. The elastic fibril, which alone normally supports the endothelium, is seen as thick wavy black lines outside the concentric rings of cells.
Weigert's resorcin-fuchsin and neutral red. Magnification ×390.

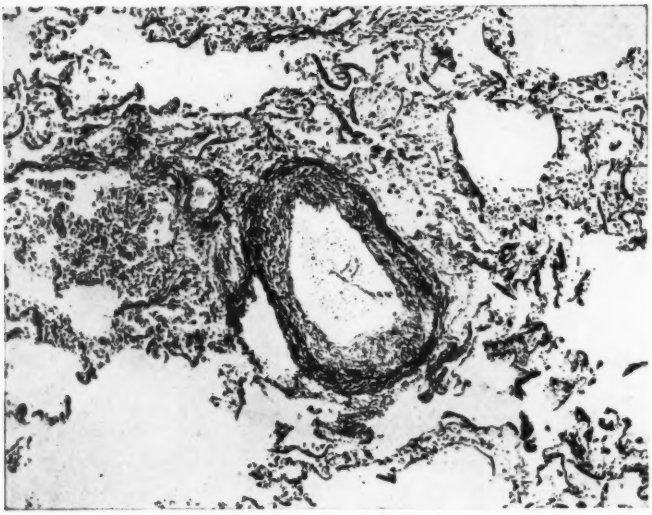

FIG. 6.—A small muscular artery. The internal and external elastic laminæ which bound the media are best seen on the left side. Weigert's resorcin-fuchsin and neutral red. Magnification ×88.

FIG. 7.—A pulmonary artery. Weigert's resorcin-fuchsin and neutral red. Magnification ×88.

at all, is very striking. Small hæmorrhages are present here and there, and many macrophages contain hæmosiderin.

Conspicuous abnormalities are present in pulmonary blood vessels of all sizes but are perhaps most notable in the arterioles and smaller muscular arteries. According to Brenner (1935) the wall of the pulmonary arterioles normally consists of endothelium supported only by a spiral strand of

elastic, but here in the affected arterioles the wall is greatly thickened and the lumen narrowed by the presence of a layer of spindle-shaped or elongated cells arranged concentrically between the endothelium and the elastic lamina (Fig. 4 and 5). The outlines of the individual cells are indistinct but in sections stained by Van Gieson's method the nuclei are set against a pale-pink background which sometimes contains a few deeper red collagen fibres. The cells are probably fibroblasts: in their appearance and staining reactions they are different from both endothelial cells and muscle fibres. Elastic fibres are not present amongst them. Sometimes their nuclei are not distributed evenly around the narrowed lumen but are arranged in two groups at opposite poles, as in the vessel shown in Fig. 6. The lesion is similar to the " hyperplastic arteriosclerosis " or " endarteritis fibrosa " of the arterioles of the kidney and other tissues in malignant hypertension; it is different from the true endarteritis obliterans of inflammation.

Great intimal thickening is also seen in many small muscular arteries in the lungs (Fig. 3 and 6). Here the thickened intima contains relatively fewer, more elongated and denser nuclei than in the arterioles, and fine elastic fibres and muscle fibres are present as well as collagen. There is no re-duplication of the internal elastic lamina. The media appears normal in structure but may be thickened, though the measurements that would be necessary to establish this have not been made.

In the larger pulmonary arteries (Fig. 7) both medial and intimal hypertrophy are conspicuous, and there is often much atheroma. The intimal thickening is sometimes of extreme degree.

The Heart and other Organs. In the heart, the fine fibrosis suspected macroscopically is not confirmed by histological examination but the muscle fibres of the left ventricle show rather wide separation. Chronic venous congestion and a subcapsular, probably adenomatous, nodule are present in the section of the liver; infarction and a cortical adenoma in the kidney. The blood vessels of all sizes in the heart, liver, and kidney are normal.

Discussion

Clinically the most striking features about this case were the steadily progressive symptoms and signs of right ventricular failure, unrelieved by rest in bed and full digitilization. Breathlessness on exertion was first noticed less than four months before death and there was not the slightest indication of lung or heart disease before this. During the last four weeks, although cyanosis and breathlessness on movement steadily increased, there was a notable absence of quickening of the pulse rate and respiratory rate at rest and there was practically no oedema.

In an analysis of 16 somewhat similar cases, Brenner (1935) states that the duration of symptoms varied from five months to five years, the average being less than two years, and that the course was steadily downhill, treatment being ineffective. In Navasquez' three cases (1940) the duration of symptoms in one was a year, in another two years and three months, and the third had been " chesty and bronchial " for a few years. In East's three cases (1940) it was two to three years in one, six years in another, and six months in the third. In Armstrong's (1940) it was four years. By comparison with these this case appears to represent an acute manifestation of the syndrome. It is possible that the stirring up of sepsis caused by dental extraction was an additional factor in precipitating failure.

On pathological grounds too there seems no doubt that this patient died of heart failure, and the hypertrophy and dilatation of the chambers of the right side of the heart together with the absence of any abnormality of the left side at once suggests increased resistance to the flow of blood through the lungs as the probable cause. The morbid changes in the lungs lend direct support to this view, for not only is there much disintegration of the alveolar walls with inevitable reduction of the capillary bed, but there is also widespread and severe disease of the pulmonary blood vessels. Both of these abnormalities would increase the resistance in the pulmonary circuit.

What is the relationship between the vascular lesions and the disintegration of the alveolar walls? The latter might cause vascular lesions by raising the pulmonary blood pressure, but on the other hand circulatory impairment due to vascular lesions might conceivably cause disintegration of the alveolar walls. It seemed to us that a comparison of the character of the vascular lesions with those known to be produced in the systemic circulation by hypertension might be helpful in deciding which were primary. As a result of such a comparison we are of the opinion that all of the vascular lesions are such as might reasonably be produced by hypertension alone, and that when compared with those seen in most patients who have died of emphysema or other disorders likely to have produced pulmonary hypertension they are of very unusual severity.

The occurrence of vascular changes of unusual severity in certain cases of systemic

hypertension is now generally recognized, such patients being said to be suffering from malignant hypertension. In a study of the structural changes in the lungs in mitral stenosis, Barker and Weiss (1936) have presented evidence of an analogous condition in the pulmonary circuit—"pulmonary hypertension with malignant sclerosis"—in which the arterioles in the lungs show hyperplastic arteriolosclerosis and, rarely, necrotising arteriolitis quite similar to the lesions seen in the systemic circulation in malignant hypertension. Though we have not found acute necrotic lesions in the blood vessels of the lungs of our patient, the resemblance of the arteriolar lesions to the hyperplastic arteriosclerosis has already been noted. It seems possible that both on clinical and pathological grounds this is a case of malignant pulmonary hypertension; that a rise of pulmonary blood pressure initiated the malignant sclerosis of the pulmonary arterioles which then exaggerated the pulmonary hypertension and set up a vicious circle. A vicious circle of this kind is probably the essential feature of malignant as distinct from benign hypertension and it explains the rapid worsening and early death of the patient.

If the vascular lesions were the result of pulmonary hypertension it is necessary to enquire how such hypertension arose. There is no satisfactory answer to this question. Undoubtedly the capillary bed was considerably reduced by disintegration of the alveolar walls, but it is impossible to do more than speculate as to whether this was sufficient to account for the hypertension and the origin of the alveolar disintegration remains a mystery. The most obvious explanation, that the patient was suffering from chronic emphysema, appears to us untenable. There was no clinical evidence of emphysema; no long history of cough or other chest trouble and none of the physical signs of emphysema, while post-mortem the existence of emphysema was not at first noticed, so slight was it. It cannot be denied that emphysema was present in the anterior borders of the lungs but this emphysema was atrophic in type, being merely part of the general disintegration of the lung, and there was no distension of the lung nor any formation of bullae. Thus the condition of the lungs was quite different from that seen in typical chronic emphysema. Furthermore Parkinson and Hoyle (1937) have shown that any gross degree of right ventricular enlargement is uncommon even in severe cases of chronic hypertrophic emphysema. In their series of 80 cases enlargement could only be demonstrated radiologically in 18 and in only 4 of these was it great. The case we are describing showed no clinical emphysema.

Summary

A patient is described who died of right ventricular failure within four months of the first appearance of symptoms. There was no previous history of heart, lung, or other disease. Progress was steadily downhill without any response to treatment.

Post-mortem, there was macroscopically conspicuous atheroma of the main pulmonary arteries and all its larger branches with great dilatation of the right side of the heart and hypertrophy of the right ventricle, the left side of the heart being normal. Emphysema was only visible along the anterior borders of the lungs and there was no distension of the lungs or formation of bullae.

Microscopically, there was conspicuous medial and intimal hypertrophy in the larger pulmonary arteries with much atheroma, and great intimal thickening in many of the small muscular arteries. Changes similar to hyperplastic arteriosclerosis of malignant hypertension were seen in the pulmonary arterioles. There was widespread disintegration of the alveolar walls without hypertrophic emphysema.

The significance of these changes is discussed.

We wish to thank Dr. Ff. Roberts for the X-ray examination, and Mr. H. P. Hudson for the photomicrographs.

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PRÆCORDIAL ELECTROCARDIOGRAMS

A COMPARISON OF CF AND V LEAD CONNECTIONS*

BY

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In the Michael Reese Heart Station, leads CF_2, CF_4, and CF_5 are used to record the præcordial electrocardiogram. This has been found to be satisfactory for ordinary clinical use (Katz, 1946). Other chest positions have been used and the chest electrode has been combined with different distant electrodes by others. Wilson and his school (Wilson *et al.*, 1944) have been recommending a special electrode to be combined with the chest electrode; this is the central terminal which connects the three limb electrodes (each through 5000 ohms resistance): the leads so obtained are called V leads. The theoretical advantages of these leads have been questioned (Katz, 1946, and Wolforth and Livesey, 1944). Præcordial electrocardiograms recorded by V leads and by CF leads obtained from chest positions 2, 4,

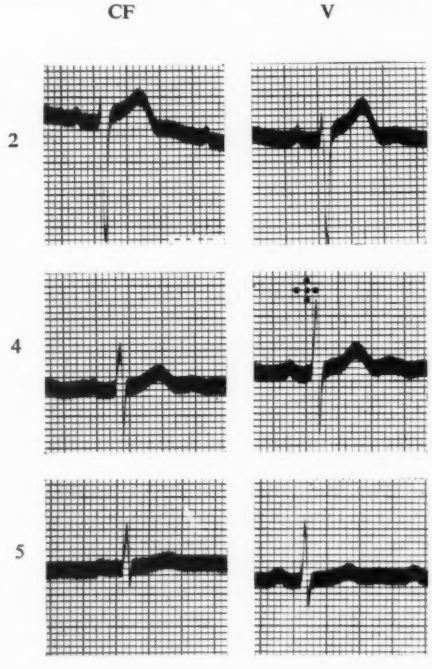

FIG. 1.—An example of CF and V leads in chest positions 2, 4 and 5, seen in about one-quarter of the normal subjects.

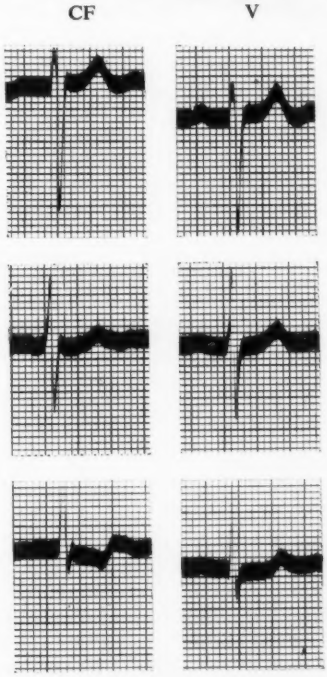

FIG. 2.—An example of CF and V leads seen in one-third of the cases with left heart strain.

* Aided by the A. D. Nast Fund for Cardiovascular Research. The department is supported in part by the Michael Reese Research Foundation.

and 5 were compared to determine how different they were from each other under various circumstances. This was done in order to determine whether or not the V leads offered any significant information of practical value not obtainable from the CF leads.

In order to make the records with V and CF comparable, they were taken immediately after one another for each of the three chest positions, the chest electrode being held in the same place while first the CF and then the V lead was taken. All records were standardized in the conventional manner, viz., 1 cm.=1 millivolt. Ninety-one cases were investigated, the first sixty being taken at random and the last thirty-one being selected to fill out the various

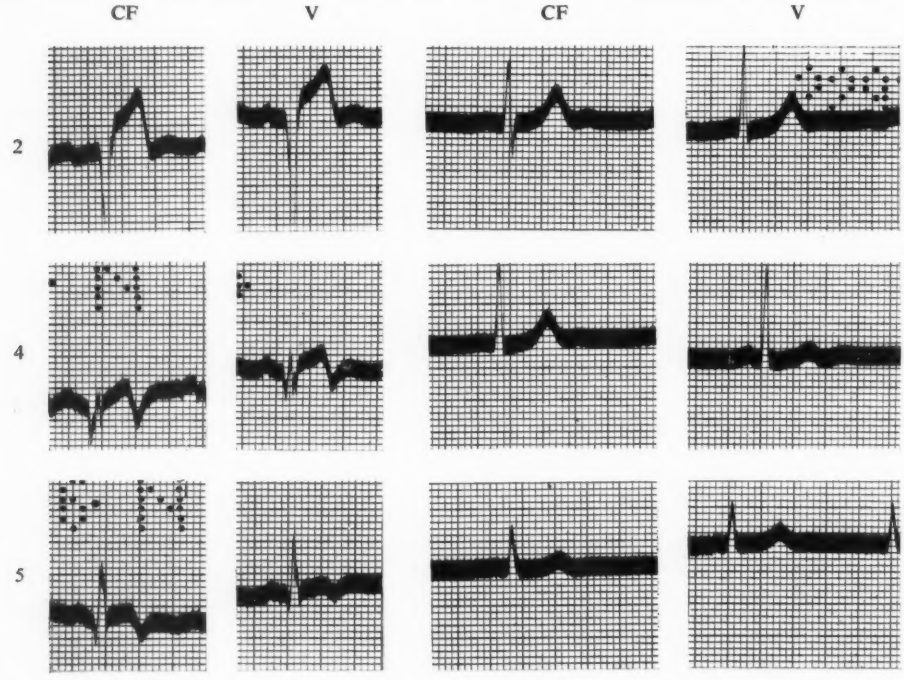

FIG. 3.—Comparison of CF and V leads in chest positions 2, 4 and 5 in subject with anterior wall infarction. Similar changes were found in about one-third of the cases.

FIG. 4.—Comparison of CF and V leads in subject with posterior wall infarction. Similar changes were found in about half the cases.

groups in which we were interested. In several instances, more than one tracing was taken on the same individual. The cases included: (1) records that were within normal limits, some with right, others with left, and still others without either axis shift; (2) records with right, left, or combined heart strain patterns; (3) records with anterior wall, posterior wall, or atypical coronary patterns; (4) records with various types of intraventricular block; and (5) records with non-specific abnormalities. Three limb and the three CF and three V chest leads were taken in every case. The diagnostic criteria for classifying the records have been described elsewhere (Katz, 1946).

The CF and V records so obtained were analyzed for the comparative heights of the various deflections, viz., P, QRS, and T as well as the deviation of the S–T junction and S–T segment. The individual phases of QRS were also compared. The data are summarized in Table I and typical differences between CF and V leads for several of these groups are shown in Fig. 1 to 4. An instance showing an extreme difference is illustrated in Fig. 5.

The salient findings of this analysis may be summarized as follows.

1. The differences between the CF and V leads were numerically greatest in position 5, least in position 2, and intermediate in position 4. Thus, more differences were found as the chest electrode was moved to the left of the midline.

2. No significant changes in the QRS amplitude and contour, or in the level of S–T segment and S–T junction were noted. In general, T tended to be more positive in V leads than in CF leads in all types of curves and P tended to be upright more often in V leads than in CF leads.

3. There were no significant differences between V and CF leads in the group of cases showing (*a*) " non-specific abnormalities," (*b*) " right heart strain " patterns, (*c*) " combined heart strain " patterns, (*d*) " atypical coronary " patterns, and (*e*) the various types of " intraventricular block."

4. In about one-quarter (16 out of 57) of the leads from records that were " within

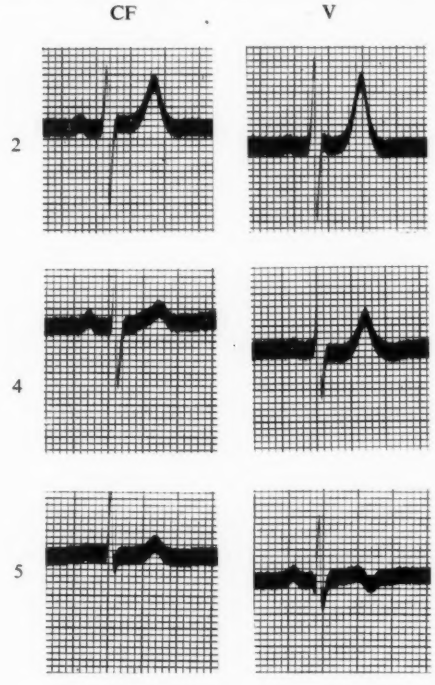

FIG. 5.—Comparison of CF and V leads showing unusual differences in subject with posterior wall infarction. These changes in position 5 occurred in one-third of the cases.

normal limits," T in V leads tended to be more upright (more positive) than T in CF leads; in the remainder, no differences were seen.

5. In the " left heart strain " pattern group there were minor to moderate differences in two-thirds (28 out of 45) of the leads. The trend was for the T waves to be more positive in V leads than in CF leads.

6. There were no differences in about one half (23 out of 45) of the leads between the T waves in V and CF leads in the " anterior wall infarction " pattern group. T was less inverted (more positive) in V than in CF in one third (15 out of 45) of the leads. Even in this group, the S–T junction and S–T segment deviations between V and CF leads were insignificant with but few exceptions.

7. In the " posterior wall infarction " pattern group, there were no differences between T in V and CF leads in about one-third (10 out of 27) of the leads. T was more negative in V than in CF in half (14 out of 27) of the leads. The tendency was for T to be less upright in V than in CF. In three instances T was inverted in V_5 while the corresponding T in CF_5 was upright.

TABLE I

DIFFERENCES BETWEEN V AND CF LEADS IN VARIOUS CONDITIONS IN 91 CASES

Chest Position	2	4	5
Records showing "Within Normal Limits": 19 Cases.			
No difference *	14	10	10
T_V more positive†	4	7	5
R_V taller	1	1	2
S_V smaller		1	3
S_V present			1
No R_V' S_V' present		1	
Records showing "non-specific Abnormalities": 10 Cases.			
No difference	6	3	1
T_V more positive	4	3	4
T_V more negative ‡		2	2
R_V taller	1		
S_V smaller		1	2
ST_V more negative			3
T_V less notched		1	
Records showing "Left Heart Strain": 14 Cases.			
No difference	7	4	3
T_V more positive	4	5	5
T_V more upright	4	3	2
T_V less inverted		2	3
T_V more negative	2		1
T_V less upright	2		
T_V more inverted			1
Q_V larger			1
Q_V smaller	2	2	1
R_V larger		1	
R_V smaller	2	1	
S_V larger	1	2	
ST_V less elevated	1	1	
ST_V more horizontal			1
Records showing "Combined Heart Strain": 3 Cases.			
No difference	2	2	2
T_V more negative	1	1	1
Records showing "Right Heart Strain": 4 Cases.			
No difference	2	2	2
T_V more positive	1	1	1
T_V more negative	1	1	1
Q_V larger	1		
R_V larger			1
ST_V more positive			1
ST_V more negative	1	1	1
S_V and S_V' smaller			1
Records showing "Intraventricular Block": 11 Cases.			
(1) Of the Common Type—4 Cases.			
No difference	2	2	3
T_V less inverted	1		
T_V more upright	1	2	1
QRS_V smaller	1		1
ST_V more elevated		1	
ST_V less depressed			1
(2) Of the S type—4 Cases.			
No difference	3	3	1
Q_V smaller	1		
T_V more upright		1	2
S_V deeper			1
(3) Of the Indeterminate type—2 Cases.			
No difference	1	1	1
T_V more upright	1		
T_V less inverted		1	
No R_V'	1	1	
R_V smaller			1
(4) Of the Uncommon type—1 Case.			
T_V less upright	1	1	1
Records showing "Anterior Wall Infarction": 15 Cases.			
No difference	10	9	4
T_V more positive	5	4	6
T_V more negative			1
Q_V present			1
R_V larger			1
S_V larger			2
S_V smaller			1
ST_V more elevated			1
ST_V less elevated	1	2	1
ST_V less depressed		1	
QRS_V larger		1	
Q_V smaller		1	1
Records showing "Posterior Wall Infarction": 9 Cases.			
No difference	5	9	3
T_V more negative	4	6	6
T_V less upright	4	5	1
T_V inverted		1	
T_V more inverted			1
T_V inverted by TCF upright			3
T_V isoelectric			1
T_V more positive	1	1	
R_V smaller	2		
S_V larger		2	1
S_V smaller		2	
ST_V more positive			3
ST_V more negative		1	
QRS_V smaller		1	1
Q_VS_V small and present			1
Records showing "Atypical Infarction": 6 Cases.			
No difference		1	1
T_V more positive	4	3	3
T_V more negative	1	2	2
R_V taller		1	2
S_V larger		1	2
ST_V more negative	4	2	3
ST_V more elevated	1		
QRS_V small	1		

* Differences in amplitude of less than 5 per cent are considered insignificant.
† More positive means either less inverted or more upright. ‡ More negative means either more inverted or less upright.

CONCLUSION

Our experience reveals that the few differences encountered between these V and CF leads were minor. It would therefore appear that the V leads offer little if any diagnostic information not obtainable in the homologous CF lead. Since the supposed theoretical advantage has been seriously questioned, there appears no reason for those accustomed to the use of CF leads to substitute the V leads.

This study was suggested by Dr. L. N. Katz, and we are indebted to him and Dr. R. Langendorf for their advice in carrying out this study.

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BILHARZIAL HEART DISEASE IN EGYPT

COR PULMONALE DUE TO BILHARZIAL PULMONARY ENDARTERITIS

BY

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Of the various pathological causes of pulmonary endarteritis and right heart failure, schistosomiasis is probably the least familiar outside Egypt and other countries where the disease is endemic. It has long been known that bilharzia ova are sometimes deposited in the lungs (Belleli, 1885; Turner, 1909), and that adult worms of *S. hæmatobium*, often coupled males and females, may be found in the pulmonary vessels (Symmers, 1905; Day, 1937). In 1928, Sorour reported pulmonary bilharziasis as a common post-mortem finding in Egypt, and described small fibrous nodules due to ova deposited in the lungs, which he named bilharzial tubercles because of their semblance to the tubercles caused by Koch's bacillus. He also described a verminous lobular pneumonia due to the presence of dead bilharzial worms, and an "endobronchitis obliterans." Under the term "bilharzial atheroma," Sorour described deposits of ova in the intima of the pulmonary vessels resulting in endothelial proliferation, and he mentioned the wealth of new capillaries in the thickened intima, since recognized as a characteristic feature of bilharzial pulmonary endarteritis. In 1932 S. Azmy Pasha, of Cairo, recorded the first case of bilharzial heart disease observed clinically and pathologically. He described two cases with cardiac enlargement, gross dilatation of the pulmonary artery and pulmonary incompetence, associated with bilharzial hepato-splenomegaly. Necropsy was performed in one case and showed deposits of bilharzia ova in the lungs, obliterative endarteritis of the small pulmonary vessels, atheroma and dilatation of the main pulmonary trunks, and hypertrophy with dilatation of the right side of the heart; in addition, there were bilharzial lesions of the bladder and cirrhosis of the liver. Similar cases were later reported by Clark and Graef (1935) in a Porto Rican and by Day (1937) in Egypt. By far the most important contribution to the subject was made by Bernard Shaw and Ghareeb (1938) who described very fully the pathological changes of pulmonary schistosomiasis with special reference to the arterial lesions and to "Ayerza's disease."

Cor pulmonale with gross dilatation of the pulmonary artery is by no means a rare clinical finding in Egypt, certainly far more common than in England. It is usually encountered in young adults suffering from advanced visceral bilharziasis (Egyptian hepato-splenomegaly) or from severe genito-urinary infection with *S. hæmatobium*. Cor pulmonale occurred in 0·8 per cent of 520 consecutive cases of visceral bilharziasis admitted to the Kasr-el-Aini Hospital, and was found in 2·1 per cent of 282 consecutive autopsies on cases of schistosomiasis (Shaw and Ghareeb). The clinical diagnosis of "Bilharzial Ayerza's disease" is not infrequently made in the wards, and cases have been shown at clinical meetings (Mousa, 1942), yet the number of cases on record, in which both clinical and pathological findings are given, is scanty. The following new case is therefore reported.

CASE REPORT

A farmer, aged 34, was admitted to the Kasr-el-Aini Hospital under Dr. Gaafar. For three years he had suffered from dyspnœa on exertion, cough with slight expectoration, and præcordial pain. For several years he had noticed hæmaturia at the end of micturition.

On examination he was breathless at rest, but not obviously cyanosed. There was no clubbing of the fingers. The neck veins were not engorged and there was no œdema. The rhythm was regular; the blood pressure, 120/80 mm. The apex was in the fifth interspace, four inches from the mid-line. There was visible and palpable pulsation in the first and second left interspaces, with dullness on percussion to the left of the sternum in this area. Auscultation showed an accentuated first sound and soft systolic murmur at the apex, and a much accentuated pulmonary second sound. The chest was emphysematous in shape, but there were no added sounds over the lungs. The liver and spleen were enlarged and firm.

X-ray of the chest (Fig. 1) showed an aneurysmal swelling in the region of the main

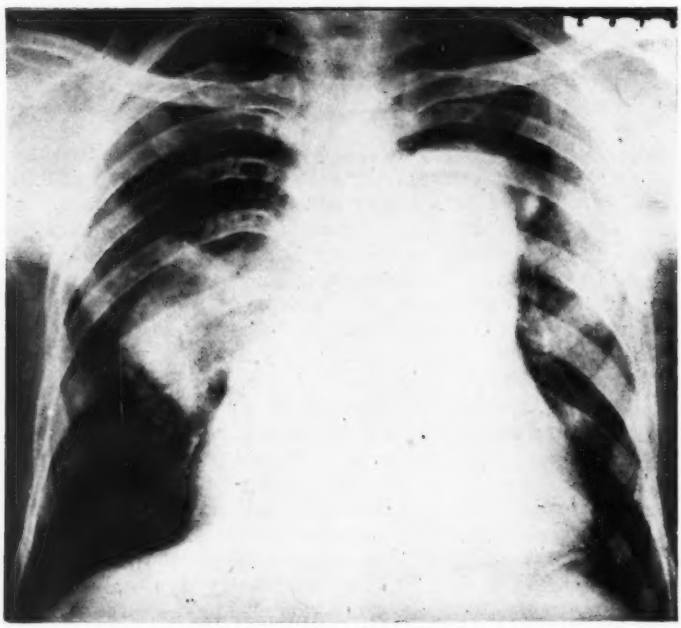

FIG. 1.—Radiograph showing aneurysmal dilatation of pulmonary artery and its right branch in the hilum. The aortic knob is invisible.

pulmonary trunk without any visible aortic knob, and the right pulmonary artery in the hilum formed a swelling of aneurysmal proportions. The heart was enlarged to right and left. There was no obvious fibrosis of the lungs. Urine contained a trace of albumin, red cells, pus cells, and living ova of bilharzia hæmatobium. The stools contained ankylostoma ova. Wassermann reaction, negative: blood-count; red cells 4,660,000; white cells 7800 (polymorphs 62 per cent, lymphocytes 26 per cent, eosinophils 10 per cent, monocytes 2 per cent).

Three weeks after admission he became suddenly worse. He complained of pain over the liver, the cervical veins became engorged, marked cyanosis appeared, and gallop rhythm was audible at the apex. The liver became more swollen, jaundice developed, and he died a few days later.

NECROPSY

Heart weight, 550 g. (approx.). The pulmonary trunk was grossly dilated, forming a sac 6·5 cm. in diameter; the circumference just above the valves was 13·5 cm. Both main branches of the pulmonary artery formed aneurysmal swellings which were almost circular, and 7 cm. in diameter. On opening up the artery, the main trunk showed thickening of its wall and intimal atheromatous plaques. The walls of both main branches were thickened and the seat of advanced ulcerated atheroma; their lumina were filled and almost occluded

by ante-mortem thrombus of some standing. Atheroma extended into the medium-sized arterial branches in the lungs (see Fig. 2 and 3).

The aorta was hypoplastic, with a circumference above the valves of 6 cm., and showed slight intimal atheroma but no evidence of syphilitic aortitis. The heart itself showed gross enlargement of the right side, both ventricle and auricle being dilated to about three times their normal capacity. The right ventricle was much hypertrophied, its wall being 1·3 cm.

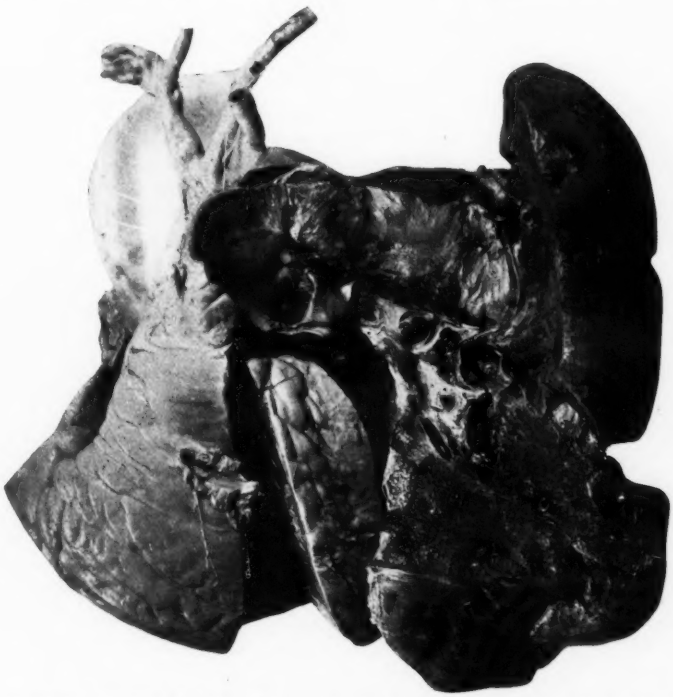

FIG. 2.—Heart and attached left lung with anterior wall of pulmonary artery and of its left branch removed to show contained thrombus.

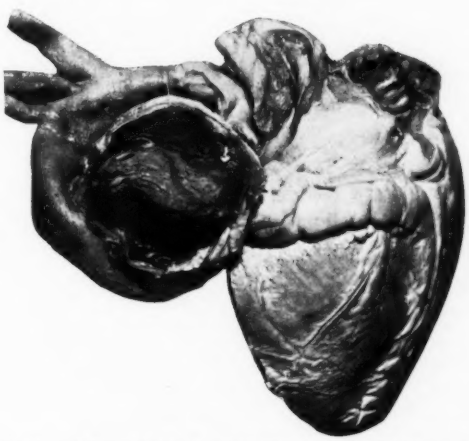

FIG. 3.—Heart and aorta viewed from right, showing aneurysmal dilatation of right pulmonary artery and occluding thrombus.

thick, and the auricle was also hypertrophied. The left ventricle was normal. All the valves were healthy, and both inter-auricular and ventricular septa were intact.

The lungs were congested but free from bilharzial tubercles. The liver weighed 1400 g.; it was coarsely granular and congested, and the naked eye appearance was suggestive of bilharzial cirrhosis. The spleen weighed 750 g.; its capsule was thickened and its pulp fibrotic. The intestines appeared normal. The bladder showed a " sandy patch " at the trigone, and ova of *S. hæmatobium* were present in scrapings. The ureters were normal and the kidneys showed congestion only.

Histology

Lungs. Sections from both lungs were examined. The alveoli were normal except for some degree of venous congestion and extravasation of red cells. The pulmonary arterioles were much thickened and showed marked obliterative endarteritis (Fig. 4). There were numerous " angeiomatoids," both of capillary and cavernous type, typical of bilharzial pulmonary arteritis (Fig. 5). Bilharzia ova were seen in relation to some of the arterioles;

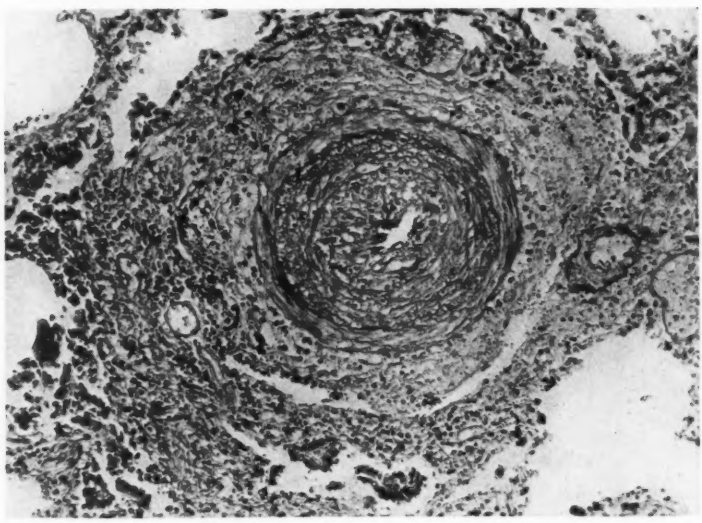

Fig. 4.—Section showing small pulmonary vessel occluded by canalized intimal thickening.

the ova were distorted and shrivelled and sometimes occupied by giant cells (Fig. 6 and 7). In the interstitial tissues, ova were scanty and calcified. Sections stained by Levaditi's method did not show any spirochætes.

Pulmonary arteries. Sections from the trunk and two main branches showed atheroma with calcification. The adventitia showed thickened vasa vasorum with perivascular infiltration by lymphocytes and plasma cells. There were minute foci of cellular infiltration in the media, but no destruction of the musculo-elastic coat suggestive of syphilis, and no spirochætes could be found in sections stained by Levaditi's method. In the main branches, there was organized thrombus of moderate age.

Aorta was normal, except for some cellular infiltration of the adventitia, and there was no evidence of a syphilitic lesion.

Liver showed periportal cirrhosis of the type usually produced by bilharzial disease in Egypt.

Spleen showed hyalinosis of the central arterioles of the lymphoid bodies. Sinusoids were filled with red cells and histiocytes. The trabeculæ were prominent and there were fibro-siderotic nodules which gave the prussian blue reaction. Bilharzial pigment both intra-

and extra-cellular was present, but no parasites or ova were seen. The histological picture was that usual in endemic splenomegaly.

Bladder and colon showed deposits of calcified ova in the submucosa.

Anatomical diagnosis. Pulmonary endarteritis due to bilharziasis; atheroma and aneurysmal dilatation of the pulmonary artery and main branches, with thrombotic occlusion. Hypertrophy and dilatation of the right heart. Cirrhosis of liver; bilharzial splenomegaly; bilharzial cystitis.

Discussion

Pathology. Adult worms may be found in the lungs where, when dead, they produce a focal verminous pneumonia, and later become calcified. The more important pulmonary lesions are, however, caused by the ova which reach the lungs as emboli from the normal habitat of the worms and become impacted in the pulmonary arterioles. In the case of *S. hæmatobium*, the ova travel direct from the systemic veins to the right heart and lungs. In the case of *S. Mansoni*, which inhabits the portal tract, ova must reach the systemic veins via collateral venous channels which develop when the liver has become cirrhotic.

Shaw and Ghareeb classify pulmonary bilharzial lesions as follows:

(1) Parenchymatous tubercles.

(2) Focal arterial lesions.

(3) Widespread arterial lesions causing " Ayerza's disease."

Ova of both *S. hæmatobium* and *S. Mansoni* infest the lungs, but the latter more often cause arterial lesions. The ova become impacted in the arterioles causing a necrotizing arteriolitis, and may then pass through the vessel wall, destroying the media, and so become extravascular, when they form bilharzial tubercles. Healing of the vascular lesion causes

Fig. 5.—Drawing of section showing angeiomatoid formation round occluded and vascularized pulmonary vessel.

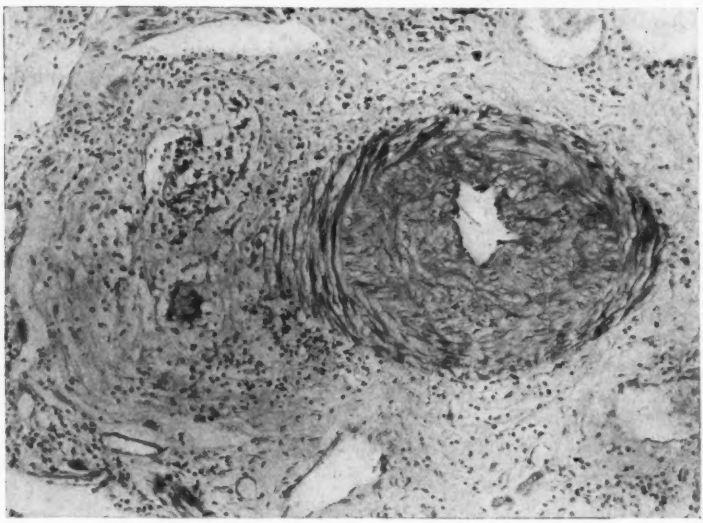

FIG. 6.—Section of thickened pulmonary vessel with adjacent giant cell filling shell of ovum.

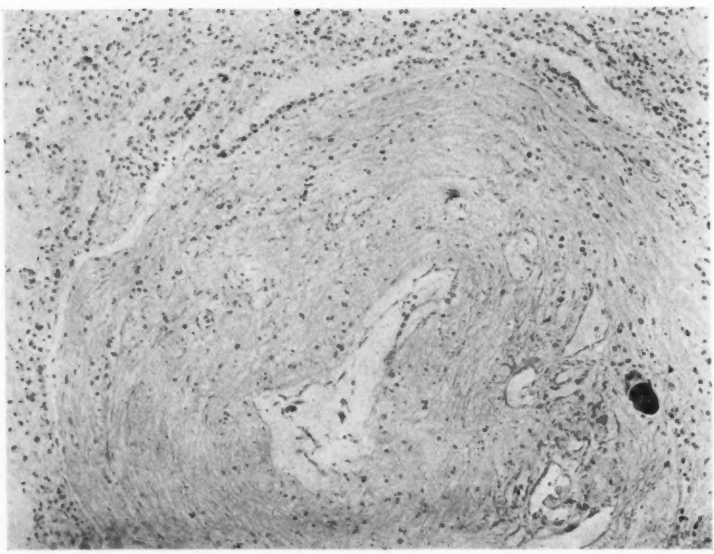

FIG. 7.—Section showing obliterative endarteritis of pulmonary arteriole, the wall of which contains a calcified bilharzia ovum and adjacent angeiomatoid formation.

obliterative endarteritis. Shaw and Ghareeb have shown that the distinctive histological feature of bilharzial arteritis in the lungs is the formation of " angeiomatoids." The occluded vessel becomes canalized by new capillaries, some of which dilate forming blood spaces lined by endothelium and, in the absence of an intact medial coat, this vascularized tissue expands beyond the normal confines of the vessel and may reach cavernous dimensions. They found no evidence that angeiomatoid formation was the result of thrombosis followed by canalization of the arterioles, for when this happens the vascular tissue is contained within an intact media. Clark and Graef (1935) also described highly vascularized tissue expanding the vessels in bilharzial arteritis of the lungs, and they too excluded canalized thrombosis as the explanation; they also noted extravascular granulomas containing endothelial lined channels. Serial sections are necessary in order to demonstrate the relation of the angeiomatoids to the vessel lumen.

In the earlier stages of bilharzial infection of the lung, ova may be seen in the vessel walls (Fig. 8) and in extravascular tubercles, but later, when there is widespread obliterative arteriolitis, and enlargement of the right heart, the ova may be scanty or absent, and angeiomatoids

FIG. 8.—Section showing bilharzia ova embedded in intima of small pulmonary vessel. (*By the courtesy of Prof. Sorour.*)

may then be the only evidence of a bilharzial ætiology. Shaw and Ghareeb believe that massive and repeated embolism of the lungs by ova is necessary to cause pulmonary hypertension and enlargement of the right ventricle.

Vessels proximal to the obstruction show medial hypertrophy and intimal thickening which is a reaction to pulmonary hypertension, and the larger branches show atheroma. Occlusion of the main pulmonary arterial branches in the hila by organized thrombus, as occurred in the present case, has also been reported in aneurysmal dilatation of the pulmonary arterial tree due to atrial septal defect (Bedford, Papp, and Parkinson, 1941); it occurred in three of Brenner's cases of primary pulmonary arteriosclerosis, and in others cited by him (Brenner, 1935). In Azmy's case of bilharzial pulmonary arteritis, one main branch was occluded by clot regarded as embolic.

While changes in the pulmonary vessels are undoubtedly the cause of the cardiac enlargement and failure in bilharziasis, the myocardium is, occasionally, directly involved, and Clark and Graef found scanty ova of *S. Mansoni* surrounded by miliary foci of fibrosis, in both ventricles. In the case of *S. Japonicum*, Strong (1944) cites a case reported from Japan in which numerous bilharzial tubercles with giant cells occurred in the ventricular myocardium, so that sections viewed by low power resembled tuberculosis.

Clinical features. In Egypt, bilharzial cor pulmonale usually occurs in young adults aged 20 to 35 years, but proven cases as young as 12 and 13 years have been recorded (Shaw and Ghareeb). The condition is encountered mainly in residents of the Nile Delta, where infection with *S. Mansoni* is endemic and where hepato-splenomegaly is prevalent. Compared with other forms of chronic cor pulmonale, the bilharzial variety affects younger subjects and does not usually cause much cyanosis or clubbing of the fingers. The absence of cyanosis has been attributed to an associated anæmia due to hookworm infestation, but even in the absence of anæmia cyanosis is seldom severe, except as a terminal event. A more probable explanation is the fact that, in bilharzialis, the pulmonary lesion may be almost confined to the arterioles, leaving the alveolar and capillary structure intact (Mousa, 1942). In fact, bilharzial lung infection may amount to a primary pulmonary arteritis, and its main effect is to cause pulmonary hypertension and hypertrophy of the right heart. In the more common varieties of cor pulmonale, the vascular lesion is associated with chronic disease of the lung parenchyma, and it is the latter that interferes with oxygenation of the blood in the lungs and thus causes cyanosis. Radiographs of the chest in bilharzial heart disease rarely show any significant changes in the lung fields apart from vascular dilatation, and evidence of fibrosis is usually lacking.

Brenner (1935), in discussing primary pulmonary vascular sclerosis states that cyanosis is usually intense, but he cites cases, including syphilitic ones, in which it was absent. In theory, provided the lesion is limited to the arterioles and the hypertrophied right ventricle can maintain an adequate flow against the increased resistance, there is no reason why cyanosis should occur; it would be expected only when the right ventricle fails. Indeed, the classical clinical picture of so-called Ayerza's disease is really one of chronic lung disease and heart failure combined.

Mainzer (1938) has described the X-ray appearance of miliary infiltration of the lung fields in pulmonary bilharziasis, but at the Kasr-el-Aini Hospital these miliary shadows in the lung fields have only been observed during the course of antimony treatment, and are regarded as due to an allergic reaction around the ova. Clinically, some degree of emphysema, with or without bronchitic signs, is the usual finding in the chest.

The radiological appearance of the heart may be indistinguishable from that of atrial septal defect. Not only is the pulmonary trunk grossly dilated, but the hilar branches may also reach aneurysmal size, a feature regarded as especially characteristic of atrial septal defect. Pulmonary incompetence from enlargement of the valvular orifice is common in both conditions.

The main diagnostic problem is, therefore, to differentiate between bilharzial and congenital heart disease. The presence of bilharzial lesions elsewhere is, of course, important. All recorded cases of bilharzial heart disease and all cases that we have observed have also had hepato-splenomegaly, and some have also had lesions of the urinary tract. The presence of ova in the stools and urine should always be sought. The blood may show an eosinophilia, but less frequently and to a lesser degree than in the earlier stages of bilharzial infection. The intradermal reaction of Fairley may be positive even when ova are no longer to be found in the stools or urine.

Summary

A case of chronic cor pulmonale with aneurysmal dilatation of the pulmonary artery, due to bilharzial endarteritis of the pulmonary arterioles, is described, and the pathological and histological findings are given.

The clinical and pathological features of the disease as it occurs in Egypt are briefly reviewed. It affects young adults, aged 20 to 35 years or even younger, infected with *S. Mansoni* or *S. hæmatobium* or both, and suffering from Egyptian hepato-splenomegaly.

Cyanosis and clubbing of the fingers are slight compared with that seen in other forms of chronic pulmonary heart disease, and clinical and radiological signs of lung disease are slight or absent. Dilatation of the pulmonary artery may amount to aneurysm, and relative pulmonary incompetence is common. The X-ray appearance of the heart is similar to that of atrial septal defect.

Pathologically, the changes are mainly vascular, and consist of an obliterative endarteritis of the pulmonary arterioles, atheroma and dilatation of the main vessel, and hypertrophy and dilatation of the right ventricle. Histologically, bilharzia ova may be identified in the walls of the small vessels and in extravascular tubercles. In the later stages, the occluded vessels become expanded by highly vascularized tissue to form "angeiomatoids," which are a distinctive feature of bilharzial arteritis.

We wish to thank Dr. M. Gaafar for permission to record the above case, and Prof. M. F. Sorour for his help with the pathological investigation and for the microphotographs in Fig. 4–8. One of us (D. E. B.) is much indebted to many Egyptian colleagues for the opportunity of seeing cases and for information about the clinical features of bilharzial heart disease.

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MECHANISM OF THE WOLFF-PARKINSON-WHITE SYNDROME

BY

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The Wolff-Parkinson-White syndrome has been described frequently during the past few years, and there is considerable evidence now that the short P–R interval associated with an aberrant QRS is probably due to short circuiting of an auricular stimulus through one or more accessory bundles.

Hunter, Papp, and Parkinson (1940) came to the conclusion that the syndrome represented a double rhythm by two interfering pacemakers, one near the sinus and the other in one bundle branch, but Wolferth and Wood (1941) raised objection to this hypothesis, and adhered to their previous theory (1933) put forward to explain this type of cardiogram, namely, that the ventricular asynchronism is due to premature stimulation of one ventricle by conduction through the bundle of Kent. Parkinson and others described gradual changes of P coinciding with gradual changes in the ventricular complex, and argued against the bundle of Kent hypothesis. Wolferth and Wood, however, thought there was as much variation between the P waves before aberrant as there was before normal complexes, and quoted a case of Tung (1936) in which the P waves became smaller and the QRS complexes normal twenty minutes after the injection of atropine; thirty minutes after the injection the P waves had returned to their normal size, while the QRS complexes still remained normal. It was suggested that the atropine may be a factor in this change in the character of the P wave. Butterworth and Poindexter (1944) suggested that fusion beats may be the explanation of the cardiographic changes in this syndrome. Rosenbaum, Hecht, Wilson, and Johnston (1945) used unipolar leads from the œsophagus, præcordium, and other parts of the thorax, and gave observations supporting the presence of one or more accessory conducting bundles. Stein (1945) described a case showing normal P–R intervals and complexes alternating with those of the Wolff-Parkinson-White syndrome immediately after cessation of attack of paroxysmal tachycardia, suggesting also a shorter accessory pathway between the auricles and ventricles. Öhnell (1944) in a comprehensive monograph "Pre-excitation—a cardiac abnormality" showed various types of this syndrome. He assumed that there were two excitatory waves, the regular impulse via the bundle of His and an additional premature ventricular spread. These sometimes varied in time in the same case, and he described this as a "concertina effect."

The following (Case 1) showed all the features of this Wolff-Parkinson-White syndrome. A boy, aged 17, was admitted to the Aberdeen Royal Infirmary on June 12, 1942, complaining of palpitation which was found to be due to paroxysmal tachycardia. He had three attacks of palpitation during the previous year, and, except for one fainting attack, after a strenuous game of football, there were no other symptoms. He gave no history of any serious illness. On physical and X-ray examination there was no abnormality of the cardiovascular system. Cardiograms were obtained showing paroxysmal tachycardia (Fig. 1), and others showing the characteristic *Sh. P–R : B.B.Bl.* syndrome—a short P–R interval and the QRS of the bundle branch type (Fig. 2). Since his discharge from the hospital in August 1942 he has had paroxysms of tachycardia, occurring at varying intervals and lasting from a few minutes to several hours. During these he had palpitation and breathlessness, but at other times he felt quite fit.

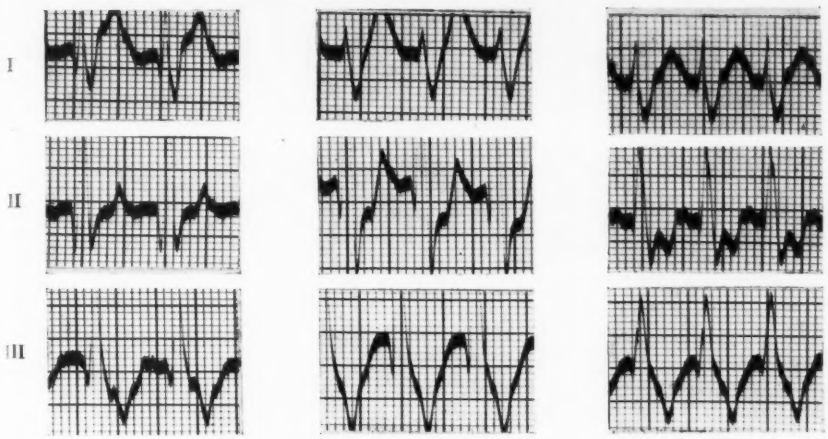

FIG. 1.—Case 1. Paroxysmal tachycardia. (A) 15/6/42. (B) 27/8/42. (C) 30 minutes after atropine.

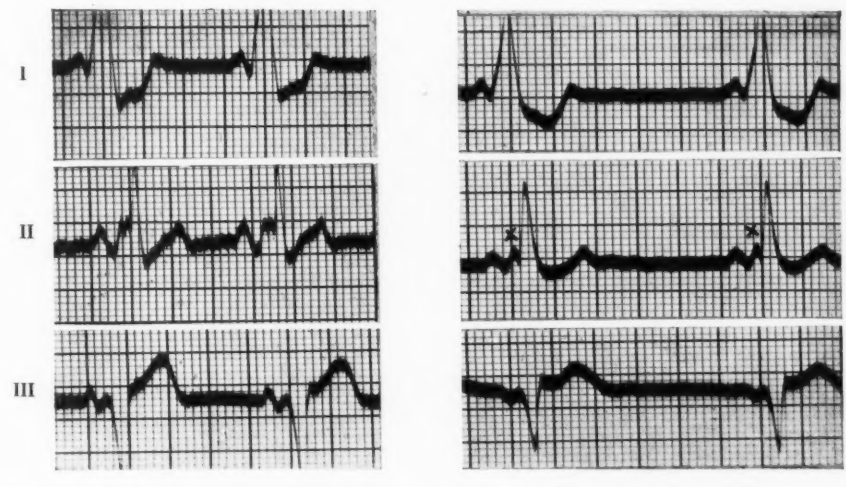

FIG. 2.—Case 1. Showing *Sh. P–R : B.B.Bl.* complexes of two different types.

CARDIOGRAPHIC ANALYSIS

The cardiograms in Fig. 2 and 3A show, especially in leads I and III, the typical short P–R interval and the widened QRS complex, somewhat resembling a left bundle branch block. Fig. 1 shows paroxysmal tachycardia, and other figures illustrate the effect of 1/50 of a grain of atropine given subcutaneously.

The following features are worthy of note.

(1) When the *Sh. P–R : B.B.Bl.* rhythm is present, the complexes are not all similar (Fig. 2 and 3A): there is a variation of P waves, of QRS complexes, and of S–T segments. This indicates variability in the path followed by the impulse over both auricles and ventricles. Öhnell (1944) would regard the differences in the complexes as due to a variation in the interval between the beginning of two assumed ventricular excitation waves.

(2) The second leads in Fig. 2B, Fig. 3A, and Fig. 5B and D show, after each P wave, another upward deflection (afterwards indicated as X) just before the QRS complex.

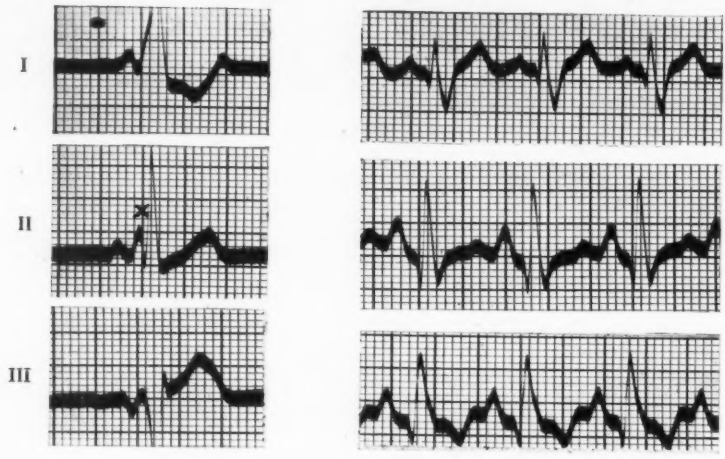

FIG. 3.—Case 1. 2/9/42. (A) *Sh. P–R : B.B.Bl.* complexes immediately before injection of 1/50 grain atropine. (B) 15 minutes after injection of atropine.

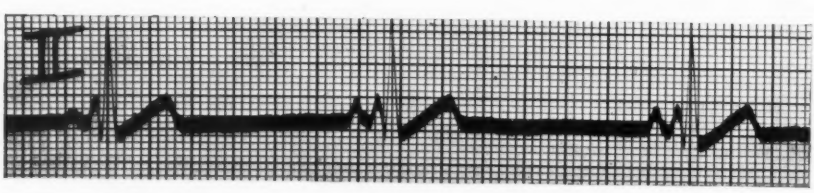

FIG. 4.—Case 1. 2/9/42. After atropine showing variation of P waves.

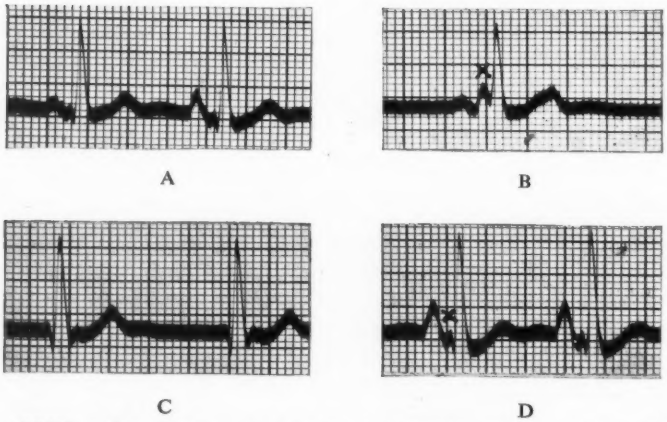

FIG. 5.—Case 1. 2/9/42. After atropine. All lead II. (A) Showing further variation of P waves. (B) Note relative size of P and X waves. (C) Showing change of pacemaker to A-V node. (D) Compare with Fig. (B). Change in size of P and X waves.

(3) The length of the P–Q interval in lead II of Fig. 3A, where the abnormal rhythm is present and the interval includes an X deflection, is equal to that of the P–Q interval in lead II of Fig. 3B. This shows right bundle branch block after atropine, but the P–R and the P–Q intervals may be considered normal. It may be noted that the configuration of QRS is similar to that in the paroxysmal tachycardia in Fig. 1.

(4) Atropine can modify the P waves and QRS complexes in many ways.

(*a*) Fig. 4, and 5A, B, and D, show P waves of varying sizes and shapes, mostly followed by X waves, which also vary.

(*b*) The P–R intervals in Fig. 5A are shorter than the assumed normal interval in Fig. 3B.

(*c*) Fig. 5C shows nodal rhythm with disappearance of P and X.

Discussion

The cardiograms suggest two special comments. The variation in shape of the P waves and the P–R intervals points to changes in the position of the pacemaker. There is room for considerable variation of its position within the sheath of muscle described anew by Glomset and Glomset (1940). Abnormal lability in its position seems to be one feature of the disorder.

Secondly, the shape of the ventricular complex in most cases of the syndrome shows two peculiarities. The first is a thickening and slurring of the initial rise of R with resultant widening of the complex; the second is an abnormality of the S–T segment tending to make the whole complex diphasic but less so than in ordinary bundle branch block. It would appear, therefore, that the excitatory stimulus to the ventricle is abnormal and also premature. This may be explained by assuming an accessory bundle joining the auricles and ventricles. If an excitatory wave from the auricles passes down the main A-V bundle, it cannot stimulate the part of the ventricular muscle that is already responding to the accessory bundle stimulation. Whether the greater or earlier stimulus to the ventricle is through the main bundle or through an accessory bundle probably depends on the position, size, and conducting capacity of the accessory junctional tissue. Assume accessory junctional tissues either on the right or left side of the main bundle (A C or B C in Fig. 6). Suppose the auricular stimulus reaches the A-V node (AV), and another point A, the beginning of the accessory junctional tissue, at the same time; if A–C is shorter or of higher conductivity than AV–C, C may be stimulated through A before the excitatory impulse from A-V arrives. There will, therefore, be a change in the cardiogram during the P–Q interval depending on the distance

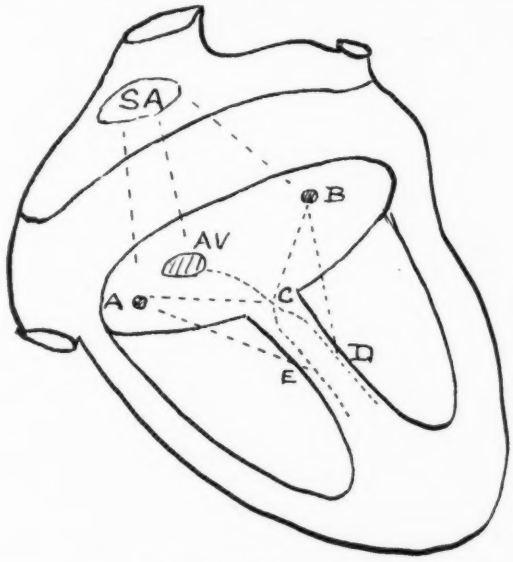

Fig. 6.—Diagram of the heart. See text.

of A and AV from C, and the rates of conduction of A–C, AV–C. The accessory junctional tissues may possibly be longer, A–E or B–D, and there would be short circuit stimulation in the region of one of the main branches, either right or left, depending on the position of the accessory conducting tissue.

The main A-V bundle is normally well insulated from the surrounding muscular tissue and the stimulus is conducted to the branches before there is response of the ventricular muscle. An accessory bundle may not be so completely insulated, resulting in infiltration of the stimulus to the ventricular muscle during the passage from A to C or A to E, and partly explaining the variation of the beginning of the QRS complex.

An accessory bundle (or bundles) between the auricles and ventricles may be the commonest cause of this early excitation of the ventricles, and in support of this theory are the post-mortem results of Öhnell (1944) and Wood, Wolferth, and Geckeler (1943), but there are other possible causes. Anatomical abnormalities occur in all tissues and an accessory branch from the bundle proximal to the main division should be kept in mind as a possible cause of pre-excitation.

In these cases of accessory junctional tissue, the auricular impulse therefore finds the shortest and easiest way to the ventricle and when the sympathetic and vagal mechanisms are stabilized, the auricular stimulation apparently pre-excites the ventricle, but if the vago-sympathetic control is changed by atropine or other drugs, the conduction capacity of junctional tissues is changed. Wilson (1915*a*) showed that even normal rhythm could be converted into auriculo-ventricular with right bundle branch block by stimulation of the vagi, and that by administration of atropine normal rhythm could be restored. He concluded that the vagi were partially responsible both for the change in the location of the pacemaker and for the abnormality of the ventricular complexes. Wilson (1915*b*) also found it possible to produce A-V rhythm in a large proportion of young persons by vagus stimulation during the intermediate period between injection of atropine and the appearance of its maximum effect, and he inferred a selective action of atropine on the vagal endings in the A-V node. The same author (1915*c*) described cases showing changes in the location of the pacemaker associated with respiration. The changes were of three kinds—migration of the pacemaker within the intermediate neighbourhood of the pacemaker, migration to the A-V node, and complete auriculo-ventricular dissociation. In the *Sh. P–R : B.B.Bl.* syndrome there is no doubt that in the majority of cases, including the first case presented above, atropine has this action on the pacemaker. Öhnell (1944) has described various ways of changing the mechanism in these cases—by carotid sinus pressure, by holding the breath, and by change of posture. Quinidine medication has also been shown to change the excitatory mechanism, possibly by its effect on the conducting tissues.

It seems, therefore, that the auricular stimulus in the Wolff-Parkinson-White syndrome is transmitted to the ventricles by the main bundle and an accessory bundle. By decreasing the vagal control, the stimuli through the main bundle are increased, and those through the accessory bundle decreased. This may be due to a relatively increased conduction capacity of the main bundle or due to a change of the position of the original pacemaker nearer the A-V node, favouring increased excitation through the main bundle.

As indicated in Fig. 6 an accessory bundle may be long (A–E) causing premature stimulation of the ventricle some distance from the main bundle and short-circuiting in the region of a branch. This type may show a cardiogram of the typical *Sh. P–R : B.B.Bl.* syndrome, but the accessory tissue may be less extensive (A–C, Fig. 6) and the premature excitation may be only very slight. Another case is given to illustrate this.

A medical man (Case 2), aged 35 years, who was being treated for pulmonary tuberculosis by artificial pneumothorax, had a severe attack of paroxysmal tachycardia in 1945. He gave the history of having similar attacks when he was a student. When he was seen soon after the paroxysm in 1945 there was nothing abnormal found on physical examination in the cardiovascular system, but a cardiogram (2/11/44) (Fig. 7) showed a small wave (X) between P and Q. On 8/11/44 (Fig. 8) the X wave was absent, but there was slurring at base of QRS. The history of attacks of paroxysmal tachycardia and the abnormality in cardiogram suggested pre-excitation of the ventricles. After atropine the slurring of QRS disappeared (Fig. 9). A cardiogram taken on 9/5/34 (Fig. 10) showed a similar abnormality at the base of QRS,

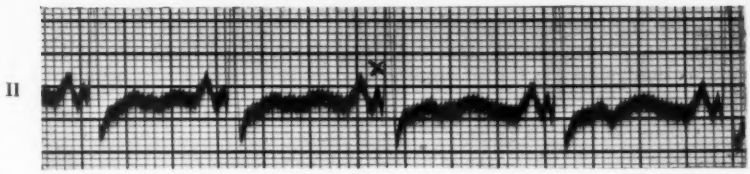

FIG. 7.—Case 2. 2/11/44. After an attack of paroxysmal tachycardia showing small X wave after P.

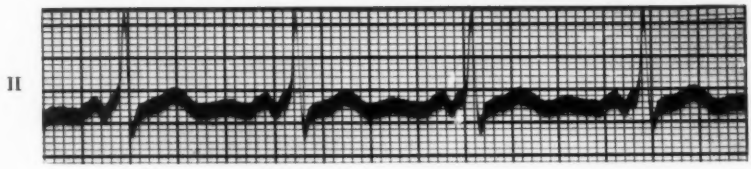

FIG. 8.—Case 2. 8/11/44. Showing slurring at base of QRS.

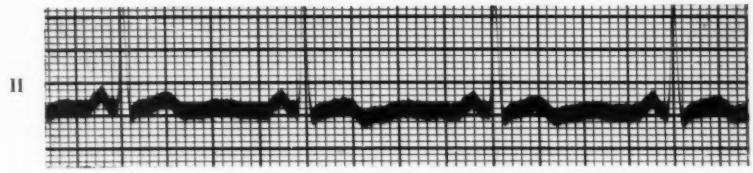

FIG. 9.—Case 2. 8/11/44. Showing disappearance of slurring after atropine 1/50 grain.

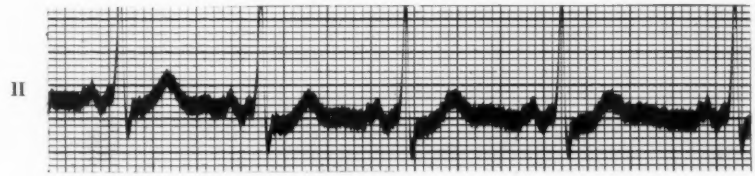

FIG. 10.—Case 2. 9/5/34. Cardiogram taken ten years previously showing abnormality at base of QRS.

showing that this pre-excitation had been present for at least ten years. This case would appear to have a minimal change in the cardiac conducting tissues (as compared with the more marked changes in the first case showing the typical *Sh. P–R : B.B.Bl.* syndrome). Pre-excitation may, therefore, vary in degree.

Doubtful cases showing slurring at the base of QR, especially if there is a history of attacks of paroxysmal tachycardia, should be investigated by means of atropine or by one of the other methods mentioned by Öhnell.

Disease or injury of the main junctional tissues may be a cause of pre-excitation of the ventricles. Accessory bundles could be present without pre-excitation showing, provided the conduction capacity of these is relatively small as compared to that of the main bundle. But if the latter is affected by disease, such as diphtheria, the auricular stimulus will tend to take the next easiest path—the accessory tissue which may be present but normally inactive. Pre-excitation of the ventricles will then result. Cookson (1945) describes a case of diphtheria showing what is almost certainly ventricular pre-excitation. If there had been no accessory junctional tissue, probably complete heart block would have occurred.

There may be little or no change in the cardiogram after the administration of atropine, suggesting that conduction through accessory tissue is more permanent or fixed and not influenced by changes in the vago-sympathetic mechanism. This is illustrated in another patient.

A girl (Case 3) aged 21, a munition worker in Coventry, was seen in the out-patient department of the Aberdeen Royal Infirmary on 6/10/44. She gave a history of attacks suggesting paroxysmal tachycardia and the cardiogram (Fig. 11A) showed a short P–R interval and broadening of the QRS complex, almost certainly due to pre-excitation of the ventricle. The maximum change after atropine is slight (Fig. 11B).

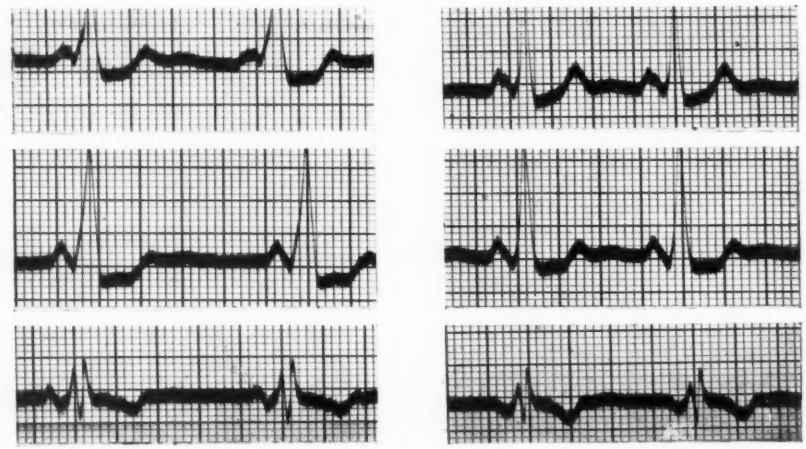

FIG. 11.—Case 3. (A) Cardiogram of girl with a history of attacks of paroxysmal tachycardia showing *Sh. P–R : B.B.Bl.* complexes. (B) Cardiogram showing only slight changes after atropine 1/50 grain.

SUMMARY

A typical case of the Wolff-Parkinson-White syndrome is described and the mechanism discussed. Premature excitation (or pre-excitation) of the ventricle is probably the cause, and published autopsy reports suggest that this is due to accessory conducting bundles between the auricles and ventricles. Other abnormalities, such as an accessory branch of the main bundle, could cause pre-excitation and should be looked for in future autopsies.

Pre-excitation may vary in degree. The degree of short-circuiting of the auriculo-ventricular conduction may depend on the position of the accessory bundle or bundles and generally changes or disappears with variation of the vagal tone.

A case has been described showing slight pre-excitation which has been present for at least ten years.

Pre-excitation is generally demonstrated by changes in the P–Q interval after injection of atropine, but a case with almost fixed pre-excitation is described.

I wish to express my thanks to Dr. W. F. Croll and to Professor R. S. Aitken for valuable help in preparing this paper. I am indebted to Dr. John Parkinson for literature and helpful criticism of an unpublished paper, and to Dr. A. Rae Gilchrist for the cardiogram of Fig. 10.

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POSTURAL HYPOTENSION

BY

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Received March 21, 1946

Postural, or better, orthostatic, hypotension was first described in 1925 by Bradbury and Eggleston. The outstanding symptom, a profound fall in blood pressure on standing up, is one of a triad. The other two, less dramatic, but none the less important and almost constantly present, are anhydrosis and impotence.

The disease is almost entirely confined to males, and only two out of twenty-four reported cases have been women. The age at which symptoms are first noted has been anything from 28 to 70 years.

Accounts of the first appearance of symptoms are not always full, but it is clear that in a fair proportion the first indication of the onset of the disease is anhydrosis; this has sometimes been there for a number of years before the symptoms of hypotension have attracted attention. Impotence appears to come later; usually with or after the hypotension.

Report of a Case

The following is an account of the investigation of a case which presented characteristic features.

J. M. was an engineer, aged 57, married, with four children. He had a severe attack of typhoid at 45; at 49 he suffered from metal poisoning: his occupation at that time led him to handle brass, gun metal, and phosphor-bronze, and sometimes he put a valve of this material in his mouth. Up to the age of 55 he still played tennis. He had felt the cold of recent years.

Syncopal attacks. At the age of 50 he began to suffer from what he called fainting attacks, which came on when he was standing up, never when sitting or lying. Before the attack he used to feel giddy and unsteady; his legs trembled and his hands began to shake, and he could no longer stand up; and he had to drop straight down and sit crouched or leaning forward holding his head down, semi-conscious. Sometimes he lost consciousness. The attack lasted several minutes; after a little he would recover and could go on walking. During the last few years the attacks had become more frequent. Apart from the giddiness, the attacks were not particularly unpleasant; there was no nausea, nor sinking feeling in the abdomen, nor sweating. Usually the attacks were more frequent in the morning than in the afternoon.

Anhydrosis. He had never sweated on his face and for the last four years has not sweated at all. For many years he only sweated on the left side of his body. This had been noted by his fellow workers, for only one side of his shirt became damp.

Impotence. About the age of 37 he became impotent and has had no sexual activity or desire since. He was never constipated.

This account is fairly characteristic of this disorder, and the observations on the blood pressure given below confirm the diagnosis.

Physical examination. A small thin man, rather bent, looking rather younger than his years. Height, 5 feet 2 inches, weight 8 stone 4 pounds. His demeanour was alert and active. His skin was inelastic and dry, with a greyish pallor. The growth and distribution of hair

was normal. His voice was high-pitched and rather piping. The testes were not atrophied. There was nothing abnormal in the heart or arteries: the skiagram of the chest was normal and so was the cardiogram. All other organs, including the central nervous system, appeared to be healthy. The Wassermann reaction was negative.

The Effect on the Blood Pressure of Changes in Posture

These observations were made with the patient lying on an electrically operated tipping-table. When tilted from horizontal to 35° head upwards in 7 seconds, the blood pressure would fall about 40 mm. systolic and 25 mm. diastolic in a minute. The heart rate remained unchanged. The results were much the same when the patient was tilted to 90° head upwards. After being upright for two minutes the systolic pressure was 50 mm., and the diastolic unreadable.

It was thus possible to study the effect of raising the angle of the body to the horizontal without movement. It was found that the main fall in pressure occurred in the first half-minute. The systolic and diastolic pressures fell about equally, though diastolic readings were hard to obtain; the rate of the heart remained unchanged. There was not much further fall in pressure when the patient was raised to 90°, instead of 45°. These passive alterations in posture caused the blood pressure to fall in much the same way and to about the same degree each time. The results were typical of numerous observations.

On tilting the patient head downwards, the pressures rose from 110/75 to 145/90 at 35° head downwards, and to 170/90 at 45°. The rate of the heart did not change. On returning the patient to the horizontal the pressures resumed their original level.

Similar results to these have been noted by many observers. There is no really satisfactory explanation for them. The blood distributes itself in the body under the influence of gravity as though the arterial bed were unprovided with a vaso-constricting mechanism. Further, this lack of adjustment in the arterial bed can be shown by raising one limb.

Effect of raising the arm. With the patient recumbent the pressure was 110/80: when the left arm was raised vertically the brachial pressure fell to 88/54. With an initial higher pressure the fall was the same. Raising the other arm did not affect the blood pressure in the horizontal arm. The fall in pressure, averaging 25 mm., is about equal to the amount of the difference in hydrostatic pressure in the raised arm and the pressure at the level of the heart.

A similar effect was noted when the arm was raised vertically when he was sitting up.

Recumbent, B.P. 85/50. Sitting up, B.P. 70/50

Pressure in arm raised to level of brain, B.P. 45/?

In Sanders' case (1931) similar readings were obtained, although in other respects this patient differed considerably, as is noted elsewhere.

Effect of postural hypotension on the secretion of urine. The tendency to low levels of blood pressure during the day affects the efficiency of the kidneys, and nocturia may be a very troublesome symptom for these patients. For the past six years this man used to pass urine five or six times at night and rarely during the day. The output of urine was recorded over a series of seven consecutive days, the night time being reckoned from 9 p.m. to 9 a.m., the patient being up during the day, and the fluid intake being left to his inclination. The output during the day varied from 10 to 22 oz.; during the night from 28 to 50 oz. Bradbury and Eggleston (1925) made similar observations.

When resting in bed the blood urea was 67 mg. per 100 c.c. The urea clearance was 53 per cent of the average maximum normal. After being up for nine hours, the blood urea was 77 mg. per 100 c.c., and the urea clearance fell to 32 per cent of the average standard normal.

In a somewhat atypical case of postural hypotension reported by Corcoran, Browning, and Page (1942) the injection of angiotonin increased the blood flow through the kidneys and the renal excretion. This is the opposite to what is usually found, as the effect is vaso-constriction in normal persons. Presumably the general vaso-constriction improved the renal flow, and outweighed any local constriction of the renal arterioles.

Effect of reducing venous return to the heart. The patient was asked to blow up a column of mercury to 30 mm., and keep it there as long as possible (Flack test). With the patient

recumbent the B.P. was 112/75 and the pulse 80. On starting the test the B.P. fell at once to 50/35 and there stayed until the end of the test. After a minute it then rose to 105/60. The pulse rate remained unchanged throughout. Woofter and Deibert (1943) have made similar observations.

The effect of this test is to raise the intrathoracic pressure and reduce the cardiac intake. It would appear that the patient was unable to adjust his arterial system to meet the diminished output. In the normal person this test causes no fall in blood pressure.

When this test was carried out with the patient inclined head downwards, MacLean and Allen (1940) noted that it could be done quite well. The reason for this must be that there is adequate venous return, or that the arterial system is well filled already. The latter is more likely: for when the test is performed by the patient standing, Laufer (1942) found that the fall in blood pressure was more severe than when sitting, or lying, when it was least. It is unlikely that diminished venous return is the sole cause of postural hypotension, as MacLean and Allen (1940) suppose, in view of other evidence.

Other Observations

Sweating. Pilocarpine (1/10 grain) was given hypodermically. Seven minutes later both axillæ were moist, and a minute later both sides of the chest were sweating, likewise the face. As pilocarpine stimulates the sweat glands or the post-ganglionic endings of their sympathetic nerve supply, the response to the drug shows that these structures are intact.

On the other hand, when the patient was put in a hot-air bath for fifteen minutes, he did not sweat. Immersion in water as hot as he could bear caused no sweating on the face. This observation suggests that the anhydrosis is due to a central lesion.

Blood counts. When he first came under observation there was some anæmia—red blood corpuscles, 3·2 million, Hb. 68 per cent, C.I. 1·07. Several blood transfusions were given, and three months later the count was 3·9 million, Hb. 75 per cent. The resting gastric juice contained no acid ; after histamine injection there was free HCl. equivalent to 42 c.c. N/10. A moderate degree of anæmia has rarely been noted in this disease.

Peripheral vasomotor reflexes. In order to get some idea of the site of the lesion in this disease, various peripheral vasomotor reflexes have been investigated. A defective carotid-sinus reflex has been thought to be a cause. Vasomotor reflexes depending on stimulation with heat and cold, and the effects of emotional and painful stimuli, have given varying results.

Carotid sinus reflex. Persons vary a good deal in their reaction to pressure on the carotid sinus. In this patient there was very slight slowing and little or no fall in pressure. Other observers have found that the rate may fall along with the pressure in the usual way (Ellis and Haynes, 1936): on the whole the fall in pressure is more notable than the slowing. Stimulation of the sinus with cyanide has produced hyperpnœa (Ellis and Haynes, 1936). It has been suggested that failure of the carotid sinus to react might lead to postural hypotension; but these results show that it is not always incapable of reacting to stimuli, and would exclude it as a cause.

Reaction to cold and other peripheral stimuli. On immersing one forearm in cold water for four minutes the systolic pressure rose in that arm from 57 to 70, the diastolic remaining below 60. There was no change in the blood pressure in the other arm. This would appear to be a local reflex action.

Ellis and Haynes (1936) found that cold caused the blood pressure to rise in one patient, and that heat caused normal reflex vasodilatation. Ganshorn and Horton (1934) found that the application of cold caused a rise in blood pressure both when sitting and standing. There was failure to respond to cold in the cases reported by Woofter and Deibert (1943) and Young (1941). Stead and Ebert (1941) found that cooling the skin and painful stimuli such as pinching the skin caused vasoconstriction. Jeffers, Montgomery, and Burton (1941) found that these stimuli had no such effect, and recorded a curious result, that heating the legs and right hand caused thermal vasodilatation in the left hand.

The variable response to these stimuli is difficult to explain. Perhaps the lesion, if central, may not involve the centres concerned; or in some persons there may be reflex

paths which do not involve the centre. These reflexes may operate through centres in the spinal cord.

Tachycardia. Although nearly all cases of postural hypotension have a pulse rate that varies but little, and does not accelerate under atropine, there are a few in whom tachycardia occurs on standing up. In Sanders' (1932) case the abrupt increase in rate was due to change in the auricular pacemaker.

MacLean and Allen (1940) noted a pronounced rise in rate in a woman who had developed postural hypotension after an extensive sympathectomy, and in a fairly typical case of postural hypotension in a woman with subacute combined degeneration of the cord. There is no mention of the effect of atropine here. Some increase in rate has been noticed on standing up by Stead and Ebert (1941), and by Jeffers, Montgomery, and Burton (1941). Further information is needed about these exceptions to the general rule, particularly as to the effect of atropine. Possibly some variation in the site of the lesion may be the cause. The effect of atropine is recorded below and agrees with that obtained by most observers; also the effect of adrenalin, ephedrine, paredrine, benzedrine, and pituitrin.

Atropine. With a hypodermic injection of 1/100 of a grain, the patient being recumbent, the mouth was dry after five minutes, but the heart rate remained steady at 84. The blood pressure rose from 85/55 to 115/80. The slight rise in blood pressure is hard to explain. Paralysis of the vagus did not cause any acceleration of the heart due to the unopposed action of the sympathetic. This is in accord with the failure of the heart to accelerate on changes in posture.

Acceleration occurs, however, from the direct effect of sympathetico-mimetic drugs on the heart.

Adrenalin. The effect of 1/1000 adrenalin solution, m. 5 injected hypodermically, the patient being recumbent, was to cause a rise in blood pressure from 130/90 to 155/100 in two minutes, and the heart to accelerate from 88 to 108; while m. 10 caused the blood pressure, recumbent, to rise to 180/120, and provoked an attack of supraventricular tachycardia lasting twenty minutes, with much tremor and pallor. The patient is evidently very sensitive to these sympathetico-mimetic drugs.

A very severe reaction to 5 minims of adrenalin solution was recorded by Korns and Randall (1937), severe cardiac pain being provoked, which had to be relieved by amyl nitrite. The effect is too short and sharp for therapeutic use.

Ephedrine. In view of the possible therapeutic effect by reason of more prolonged action, the effect of half a grain of ephedrine by mouth was noted. The patient was sitting with the arm dependent. After thirty seconds the blood pressure rose from 78/50 to 120/70, the heart rate rising from 84 to 98. At the end of four hours the blood pressure was 120/90 and the heart rate 96.

As far as the sitting posture went, there was considerable improvement, and the patient felt well. The effect while standing was less beneficial. Although after the administration of half a grain by mouth the pressure when lying rose to 170/105 from 148/98 in 35 seconds, the rise on standing was to 96/68 from 62/45 in the same time. After two hours the pressure, recumbent, was 155/105; while the standing pressure was 60/—, the diastolic being unreadable.

Ephedrine stimulates the smooth muscles of the arterioles directly; the effect in this patient, when recumbent, is unusually strong and prolonged considering the dose. It is clear that the vasoconstriction is not adequate to prevent a fall of pressure on standing. But the usual tendency for pressure to rise when recumbent is augmented to a considerable degree. But caution is required with ephedrine, for unpleasant effects have been recorded (Sanders, 1932).

Paredrine. The effect of paredrine was observed. The oral administration of 20 mg. caused the blood pressure to rise from 45/10 to 70/50 in about an hour and a half while standing. Lying, the pressure rose from 80/50 to 135/110 in the same time. It would appear to be less effective than ephedrine.

Benzedrine. The observations show a considerable pressor effect, especially when recumbent. There was also a subjective feeling of improvement. A total of 60 mg. was given in the course of eight hours. The sitting blood pressure rose from 70/40 to 170/120. The

standing pressure rose from 35/20 to 100/70. There was a considerable feeling of elation. The pulse rate rose from 88 to 102. Five hours later the effect had worn off.

The effect of this drug is unusually intense and prolonged, and similar in this respect to the others of this group. A smaller dose of 22·5 mg. given in two hours caused the standing pressure to rise from 60/50 to 105/85; the sitting pressure from 70/54 to 145/115, and the lying pressure from 120/95 to 180/130. The first two doses of 7·5 mg. produced but little effect.

Pituitrin. Stimulating the unstriped muscle of the arterioles caused slight rise in blood pressure, and slight acceleration, as one might expect: 0·3 c.c. caused the blood pressure to rise, when recumbent, from 90/55 to 125/90 in two minutes: the pulse rate rose from 70 to 90.

Sweating. The anhydrosis is sometimes unilateral, as it was in this case, the right side being affected thirteen years before the other. The statement that he had never sweated on his face may be inaccurate, or may indicate that the lesion began quite early in life. Ghrist and Brown (1928) noted unilateral anhydrosis several years before the other symptoms. In Laplace's case (1942) the sweating was intermittent, apparently varying with the blood pressure: when the pressure could be made to rise, as in exercising the muscles of a limb to which a tourniquet had been applied, sweating returned. Korns and Randall (1938) found that when large doses of benzedrine were given sweating returned. There was, however, no response to pilocarpine (1/8 of a grain) given by mouth.

There was a return of sweating in a patient of MacLean and Allen (1940) who was treated by raising the head of the bed; this appeared to be accompanied by improvement in the reaction of the blood pressure to standing. A tendency to increased sweating on one side of the body while sitting still was noted by Riecker and Upjohn (1931).

In nearly all cases the sweat glands, or the autonomic nerve endings in them, respond to pilocarpine. The erratic distribution of the areas of anhydrosis needs further study in orthostatic hypotension. It may be that in the hypothalamus, lesions occur that correspond to certain body areas. The unilateral anhydrosis suggests this, and more detailed delineation of these areas might be profitable. The suggestion that the level of the blood pressure may affect sweating is interesting, but there may be actually improvement in parallel functions.

Impotence. Loss of libido and sexual activity is recorded in almost all the male cases; this has occasionally appeared as quite an early symptom. Benzedrine produced an improvement according to Korns and Randall (1938). As some of the patients have had such diseases as tabes dorsalis the defect may have been due to this cause, apart from the lesion peculiar to hypotension; but as it occurs in others with no apparent lesion of the central nervous system, it may be due to a hypothalamic lesion. Much more information is needed about the pathogenesis of this symptom.

Nature of Postural Hypotension

There is no control of the distribution of the blood in the arterial system. The blood behaves as though the arteries had no vaso-constrictor control. When the patient stands up blood tends to pool below the level of the heart. But Stead and Ebert (1941) have shown that the proportion of the total blood volume contained in the legs in cases of postural hypotension agrees closely with that present in normal persons. The conclusion is that an excessive degree of pooling does not occur. If the normal tendency to pooling be prevented by putting tourniquets on the legs, the brachial pressure does not fall in these patients. In the same way the application of external hydrostatic pressure by standing the patient in water up to the heart will prevent the pressure falling. Stead and Ebert (1941) conclude that the cause of this disorder is an "abnormal response to the pooling of a normal quantity of blood." The nature of this abnormal response has been investigated by these observers by noting that the flow of blood in the hand did not decrease as the pressure fell. This would point to a failure in the compensatory vaso-constriction, which in the normal person prevents a fall in blood pressure on standing up. Jeffers, Montgomery, and Burton (1941) confirmed that the flow of blood in the fingers of a patient with postural hypotension did not decrease on standing up, as it does in normal persons.

The rise in blood pressure which occurs in the arm when the patient is tilted head downwards shows that there is lack of control over the distribution of the blood. The fall in

blood pressure in one arm when the limb is raised, the patient being recumbent, illustrates, in one limb, what occurs in the body as a whole.

Site of the lesion. The peripheral vessels can be made to constrict by the action of vaso-constrictor drugs, so the defect does not lie in their musculature nor in their sympathetic nerve endings. In most cases vaso-constrictor reflexes acting through the sympathetic ganglia, such as may be elicited by painful stimuli, are intact. Changes of temperature in other parts of the body still cause vaso-dilatation or constriction elsewhere.

The failure in postural vaso-constriction is associated with a fixed heart rate in the large majority of cases, as shown by the inability to accelerate under atropine, or when the blood pressure falls. With this are associated anhydrosis and impotence. To account for this triad it seems necessary to look for some central site. Ellis and Haynes (1936), Wooften and Deibert (1943), and Young (1941) have stressed the association of this disease with diseases of the central nervous system, such as tabes dorsalis and encephalitis. The general consensus of opinion seems to be that the hypothalamus is the most likely site. So far there is no post-mortem evidence on the subject. The lesion must vary in extent and site, so that one can account for the exceptional cases in whom there is tachycardia on standing.

Apart from the central site, there are patients in whom there have been lesions of the cord such as hæmatomyelia, syringomyelia, and transection. Here it may be argued that either the afferent paths or the efferent paths might be interrupted. Very extensive sympathectomy may produce a similar result.

Treatment and Prognosis. This is not very satisfactory and at the most is only palliative. Following the observation that the patient was usually better in the latter part of the day, perhaps because some sort of adjustment had been achieved, MacLean and Allen (1940) have advocated sleeping with the head of the bed raised, so that the patient was never really horizontal. In the patient here described this made no difference; but he was unusual in being but little better towards evening in any case.

Bandages and binders are not practical if used so that they really check the tendency to pooling.

Patients seem to have to reduce exertion to a minimum in warm weather, and to avoid standing still. Shifting the feet and shuffling movements (Croll and Duthie, 1935) seem to lessen the tendency to fall in pressure.

Drugs. The vaso-constrictors have a certain value. That they cause a considerable rise in pressure in some cases when recumbent has been shown. In fact, adrenalin tends to be too violent in its action.

In spite of the rise in pressure when the patient is lying down, the fall still occurs when he stands up. But nevertheless, the effect on the patient is less, and the fall may be less severe. They are therefore worth while. The choice seems to lie between ephedrine, paredrine, and benzedrine. For the patient described a combination of benzedrine 5·0 mg. at 8, 9, and 11 a.m., and ephedrine 30 mg. at 1, 3, and 5 p.m., seemed to work best and helped him to get through the day fairly well. It is best to give the benzedrine early, as it seems to induce a feeling of well-being soon in the day and does not cause insomnia. Korns and Randall (1938) gave 80 to 100 mg. of benzedrine in the morning and paredrine 40 mg. every two hours till 2.30 p.m., up to 160 mg. By this means sweating and sexual activity returned.

Prognosis. The disease appears to run a prolonged course. Having reached a certain degree of severity it does not become worse. There is so far no record of fatal results. It would be interesting to know what has happened to those patients described ten years ago or more. In some instances the associated disease of the nervous system may be of a progressive character. Laplace (1942) described a case with a prolonged remission.

Summary

A case of orthostatic or postural hypotension is described.

Observations are recorded on the effects of posture on the brachial blood pressure.

The effects of sympathetico-mimetic drugs are recorded.

The stability of the heart rate under atropine and on changes in posture is noted.

The nature of the defective vasomotor control is discussed and the possible site of the lesion.

Attention is drawn to the associated symptoms of anhydrosis and impotence, which form a triad.

Benzedrine and ephedrine provide palliative relief.

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CARDIOVASCULAR DISEASES IN THE BRITISH ARMY OVERSEAS

BY

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The writers of the present communication have, during three years with British Military Hospitals in North Africa, Greece, and Italy, dealt with very large numbers of sick. In a certain period of 27 months, 9824 in-patients came under the charge of one of us (K.S.S.), while during a period of 23 months the other (R.A.M.) has examined 1431 out-patients. As we have both been impressed by the infrequency of cardiovascular disease and disorder, particularly in contrast with the incidence in the First World War, we have undertaken a survey of the number and varieties of these conditions in each of these groups.

Material and Period of Survey

Upwards of 11,000 patients have been observed in more than one hospital, but in no case was the hospital one to which cardiovascular cases were specially directed. During the 8-months' period from April to November 1944 there was another hospital in the vicinity at which electrocardiographic examination was available, but the quarterly returns showed that this caused no alteration of the average incidence of cardiovascular disorders among our patients. Our figures are therefore derived from unselected sources. Moreover, as there is no kind of heart disease or disorder in which climate or other regional variable would be likely to influence incidence in adults, the figures are probably representative of the general incidence in the British Army overseas. Foreign service in itself might be regarded as an influence favouring functional cardiovascular disorder so that our figures are possibly not representative of the British Army as a whole.

The patients with which this survey is specially concerned are those afflicted with primary organic heart disease such as mitral stenosis, or syphilitic aortitis, and those with functional disorders such as effort syndrome or vaso-vagal syncope. A further group necessarily came under consideration; these were the patients with cardiac disorders due to some underlying non-cardiac disease. Conditions under this heading were the acute myocarditis of diphtheria, and the acute left ventricular failure sometimes seen in acute nephritis. Lesions partly arterial or venous, such as trench-feet or thrombo-phlebitis, have been excluded from this survey. Typhus, in spite of its impact upon the cardiovascular system, has also been excluded.

The period which has come under consideration for in-patients is that from July 1, 1943, to September 30, 1945—27 months. The first six months of 1943 were exceptional in that the hospital organization was overburdened with great numbers of battle casualties and the large influx of those sick with malaria and dysentery. These circumstances, although they would lend additional point to our figures, have led us to start the survey from July 1943. The period over which the 1431 out-patients have been seen is from December 1942 to November 1943 and from November 1944 to November 1945.

Observations

The Table shows the numbers of cases of various diseases and disorders occurring in each period of 12 and 15 months. It will be seen that among a total of 9824 in-patients there were only 42 cases of organic cardiovascular diseases and 23 cases of functional circulatory

disorders. The total of 65 patients represents an incidence of 0·66 per cent. There were, in all, 5 patients with cardiac disorders secondary to diphtheria or nephritis, and if these be included the total is 70 patients, an incidence of 0·71 per cent.

An analysis of the 42 patients with organic disease shows rather more than half (23) to be hypertensive or degenerative, rather less than a third (13) rheumatic, 3 syphilitic, and 1

TABLE

INCIDENCE OF CARDIOVASCULAR DISORDERS AT BRITISH MILITARY HOSPITALS IN THE MEDITERRANEAN THEATRE

Diagnosis	In-patients (9824)			Out-patients (1431)		
	July 1, 1943, to June 30, 1944	July 1, 1944, to Sept. 30, 1945		Dec. 1942 to Nov. 1943	Nov. 1944 to Nov. 1945	
Effort syndrome	9	2		17	4	
Vaso-vagal syncope ..	4	4		0	0	
Paroxysmal tachycardia ..	2	0		0	0	
Left mammary pain ..	0	2		3	2	
Total " functional " ..	15	8	=23	20	6	=26
Mitral stenosis	3	2		2	1	
Aortic valve disease ..	1	4		0	0	
Mitral and aortic disease ..	1	1		1	0	
Rh. pericarditis and carditis	0	1		0	0	
Syphilitic aortitis	0	2		1	1	
Aortic aneurysm	0	1		0	0	
Hypertension	6	9		3	1	
Effort angina	0	2		0	0	
Cardiac infarction	0	4		1	0	
Arteriosclerosis	2	0		0	0	
Congenital heart disease ..	0	1		1	0	
Pericarditis (non-rheum.) ..	0	2		0	0	
Total " organic " (primary)	13	29	=42	9	3	=12
Diphtheritic myocarditis ..	1	2		—	—	
Left ventricular failure in nephritis	2	0		—	—	
Total " organic " (secondary)	3	2	=5	—	—	—
Total all cardiovascular—		In-patients	=70	Out-patients	=38	
Total all patients of same period		(I.P.)	=9824	(O.P.)	=1431	
Cardiovascular cases: percentage of total		(I.P.)	=0·7	(O.P.)	=2·7	

congenital. The remaining 2 were cases of non-rheumatic pericarditis. Of the 23 functional cases, half (11) suffered from effort syndrome, 8 from vaso-vagal syncope, 2 from paroxysmal tachycardia, and 2 from left mammary pain.

A further analysis of these figures in terms of incidence earlier or later in the 27 months is of interest. A dividing line at June 30, 1944, gives a total of 5740 patients under review before and 4084 after this date. During the earlier period there were 15 cases of functional and 8 of organic disease; whereas during the later period there were only 8 cases of functional disorder compared to 29 patients with organic disease.

The second part of the table shows the occurrence of cardiovascular disorders among out-patients during two periods; the first from December 1942 to November 1943, the second from November 1944 to November 1945. In the first period, of a total of 1125 cases, only 29 (2·5 per cent) suffered from cardiac syndromes. In the second period, the incidence was 9 out of 306 patients (3·0 per cent). This total of 38 patients represents a percentage of 2·7 per cent. The difference in the total numbers seen in the two periods is due to the fact that during the first period a number of Infantry and General Reserve training depots were in the neighbourhood.

In the first period, 20 were functional and 9 organic, and in the second period, 6 were functional and 3 organic—thus in each group two-thirds of the patients had functional disorders. Clearly the somewhat higher incidence of cardiac disorders in out-patients as compared with in-patients is accounted for by the greater numbers of functional disorders not requiring admission in this class of patient.

Comments and Discussion

The most remarkable thing about the figures in general is that they are so low. More conspicuous still is the infrequency of functional cardiovascular disorders; a total of 49 among 11,255 in- and out-patient sick is astonishingly small when it is remembered that in the war of 1914–18 disturbance of the cardiovascular system was of major importance—one case being observed for every four men wounded—and the group as a whole being second in dimensions only to pulmonary diseases among medical disorders (Lewis, 1940).

Lewis also states that 70,000 men had reported sick and been classed as cardiovascular by the summer of 1918. Among pensioners were 44,000 cases of " effort syndrome." The official history of the Great War gives 36,569 as the number of men discharged from the Army and Navy, up to May 1918, on account of cardiovascular disorders; it also claims that the true numbers of those reporting sick with cardiac symptoms must have been much in excess of Lewis' calculation of 70,000.

That functional disorders exceeded the organic during the war of 1914–18 was also indicated by the figures of Parkinson (1916). Among 90 consecutive soldiers reporting sick with symptoms suggestive of heart disease at a Casualty Clearing Station 28 had organic disease (almost all valvular) compared with 40 with " so-called soldier's heart." The remaining 22 cases were non-cardiac.

Wood (1941), investigating these cases at an Effort Syndrome Unit, referred to the fact that there were but two special centres in England and one in Scotland; working at the largest of these he had dealt with no more than 700 during the first 20 months of the war. In the Middle East Force, from 1941 onwards, all cases of effort syndrome were sent to one centre for disposal. At this centre 338 cases were observed by Hill and Dewar (1945) between July 1941 and February 1945.

The few cases of functional disorder dealt with in hospital in the present series show that medical officers are alive to the fact that patients with symptoms of this kind do not respond well to treatment as in-patients, and may be even the worse for it. Doubtless, the increased understanding of the psychogenic basis of this disorder has enabled doctors, at all stages in the soldier's career, to avoid fanning the spark of their malady into the full flame of a doctor-made disorder. The diminishing number of these cases with the passage of time may be due to the fact that the initial conditions of active service would be more likely to produce this type of psychosomatic response, and also to the increasing awareness of medical officers of the correct disposal of such cases as they developed.

To the small number of patients with cardiac neurosis must be added a considerable number who broke down with its counterpart in other systems. It may be that the numbers treated for " exhaustion " at forward centres and invalided on the score of anxiety state and psychopathic personality far exceeded any corresponding groups in the war of 1914–18.

The rising incidence of organic disease contrasted with the diminishing frequency of the functional; although the second (later) period under review comprised substantially fewer patients (4084 to 5740) there was a more than threefold increase in cases of organic cardiovascular disease. This trend suggests that with the prolongation of the war to three, four, and five years, hypertensive and degenerative changes had time to develop as a result of continuing stress and strain in those constitutionally prone to them; at the same time, the army of this later stage will have comprised a greater proportion of men in the higher age-groups.

A few general comments follow.

(1) The remarkable low incidence of cardiovascular disorders in the Army (less than 7 per 1000 of all sick admitted to hospital) reflects much credit on Recruiting Medical Boards who succeeded in eliminating at this stage the vast majority of patients with organic cardiovascular disease and to a large extent weeding out those prone to effort syndrome and other

neuro-circulatory upsets. Analysis of effort syndrome cases of 1914–18 showed that 43 per cent had had symptoms on enlistment (Lewis, 1940).

(2) A total of 17 cases of rheumatic heart disease was a very small number. These cases are generally not hard to detect at routine recruiting examinations. The cases encountered in this series no doubt included some whose signs were very slight two or three years previously when they joined up. The physical stress of army life and campaigning might be expected to accelerate the natural diminution of the cardiac reserve. A majority of the patients with rheumatic valvular disease presented with gradually increasing breathlessness on exertion.

(3) Apart from the low incidence of rheumatic heart disease, the incidence of acute infective polyarthritis of all types was astonishingly low when the living conditions of the men are remembered (only 62 cases, or 0·6 per cent of all in-patients). Both in the winter and spring of 1943 in North Africa, and in the same seasons in Italy in 1944, the front-line soldiers were subjected to prolonged exposure to wet and cold. Among the very few acute arthritic illnesses encountered there was only one case in which valvular disease developed in a heart believed to be previously healthy. In this man of 24 years acute polyarthritis was succeeded by pericarditis and thereafter an aortic diastolic murmur was heard for the first time.

(4) Only two cases of congenital disease were encountered. The first was an unobtrusive one, and a condition (dextrocardia) that might easily be passed over among large numbers of examinees, and it might be added, appropriately so. The second was pulmonary stenosis with few signs that may well have progressed under active service conditions.

(5) Certain cardiac disorders secondary to diseases which are not uncommon have a special significance in active service conditions.

(*a*) *Diphtheria.* This disease is common in the army overseas. Fortunately, acute diphtheritic myocarditis is a rare event owing to the insistence among medical officers on large and early dosage with anti-diphtheritic serum even in suspected cases, and appreciation of the paramount necessity for at least four weeks rest in bed. Special risks exist in that diphtheritic infection of septic sores or abrasions carry the same threat to the heart as faucial infections but are more insidious in their development of circulatory and neuritic complications and are more likely to escape correct diagnosis. For example, during active operations a patient may be admitted for treatment of injuries the severity and priority of which detract attention from an indolent painless sore in which diphtheritic infection has supervened, until myocarditis or neuritis are far advanced.

(*b*) *Acute nephritis.* It is well known that acute left ventricular failure with paroxysmal nocturnal dyspnœa sometimes develops in the course of acute nephritis, particularly when the hypertension is conspicuous or sustained. This complication has twice been encountered in the present series, in patients with acute nephritis whose principal complaint was waking in the night short of breath. The onset with this symptom might be related to the more strenuous life of the average soldier compared with the average civilian.

(6) During the period under review the number of in-patients with lobar or bronchopneumonia was 100. It is known from morbid histological studies that myocarditis may complicate these diseases (but not primary atypical pneumonia). However, in no case was there evidence either of myocarditis or of right heart failure. Nor did secondary pericarditis ever develop. This result is surprising when the conditions under which they were taken ill, and the consequent likelihood of a severe infection, are borne in mind.

(7) Certain unusual conditions may be contingent on active service. For example, in 1943 in North Africa when prophylactic mepacrine was first instituted, a medical officer developed auricular fibrillation in the course of gastro-enteritis that followed the third dose of 0·2 g., the doses being at 4-day intervals. After some hours the arrhythmia disappeared. The patient had a healthy heart, and he has had no such disturbances in the two years that have since elapsed.

Summary

An investigation has been made of the incidence of cardiovascular disorders among British soldiers overseas.

A survey of 9824 consecutive admissions to a Medical Division, and of 1431 consecutive soldiers attending an out-patients' clinic, has been made.

Among the 9824 in-patients there were 70 cases of functional or organic cardiovascular disorder, an incidence of only 0·71 per cent. The organic disorders were about twice as frequent as the functional. During the later part of the 27-months' period, there was an increasing ratio of organic to functional disorder.

A total of 38 patients with cardiovascular disorders were observed among the 1431 out-patients (2·7 per cent). Approximately two-thirds of these patients had functional conditions and one-third organic lesions.

Effort syndrome never represented an important medical disability owing to (i) efficient selection by Recruiting Medical Boards, and (ii) better understanding of the appraisal and disposal of cases at their inception by army medical officers. The infrequency of effort syndrome contrasted sharply with its high incidence in the war of 1914–18.

Heart conditions have very rarely been initiated by rheumatism acquired on active service. Among many cases of pneumonia there were no examples of myocarditis.

The special significance of diphtheria and nephritis as causes of cardiovascular disorders in military practice is discussed.

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